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(54) Title: UREA DERIVATIVES AS KINASE MODULATORS

(57) Abstract: The invention provides methods and compositions for treating conditions mediated by various kinases wherein derivatives of urea compounds are employed. The invention also provides methods of using the compounds and/or compositions in the treatment of a variety of diseases and unwanted conditions in subjects.

UREA DERIVATIVES AS KINASE MODULATORS

This application claims priority to US Provisional Application No. 60/520,273, filed November 13, 2003, US Provisional Application No. 60/527,094, filed December 3, 2003, US Provisional Application No. 60/531,243, filed December 18, 2003, and US Provisional Application No. 60/531,082, filed December 18, 2003, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND

Protein kinases (PKs) play a role in signal transduction pathways regulating a number of cellular functions, such as cell growth, differentiation, and cell death. PKs are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins, and can be conveniently broken down into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs). Growth factor receptors with PTK activity are known as receptor tyrosine kinases. Protein receptor tyrosine kinases are a family of tightly regulated enzymes, and the aberrant activation of various members of the family is one of the hallmarks of cancer. The protein-tyrosine kinase family, which includes Bcr-Abl tyrosine kinase, can be divided into subgroups that have similar structural organization and sequence similarity within the kinase domain. The members of the type III group of receptor tyrosine kinases include the platelet-derived growth factor (PDGF) receptors (PDGF receptors α and β), colony-stimulating factor (CSF-1) receptor (CSF-1R, c-Fms), FLT-3, and stem cell or steel factor receptor (c-kit). A more complete listing of the known Protein receptor tyrosine kinases subfamilies is described in Plowman et al., DN&P, 7(6):334-339 (1994), which is incorporated by reference, including any drawings, as if fully set forth herein. Furthermore, for a more detailed discussion of "non-receptor tyrosine kinases", see Bolen, Oncogene, 8:2025-2031 (1993), which is incorporated by reference, including any drawings, as if fully set forth herein.

Hematologic cancers, also known as hematologic or hematopoietic malignancies, are cancers of the blood or bone marrow; including leukemia and lymphoma. Acute myelogenous leukemia (AML) is a clonal hematopoietic stem cell leukemia that represents ~90% of all acute leukemias in adults. *See e.g.*, Lowenberg et al., *N. Eng. J. Med.* 341:1051-62 (1999). While chemotherapy can result in complete remissions, the long term disease-free survival rate for AML is about 14% with about 7,400 deaths from AML each year in the

United States. The single most commonly mutated gene in AML is FLT3 kinase. *See e.g.*, Abu-Duhier et al., *Br. J. Haemotol.* 111:190-05 (2000); Kiyoi et al., *Blood* 93:3074-80 (1999); Kottaridis et al., *Blood* 98:1752-59 (2001); Stirewalt et al., *Blood* 97:3589-95 (2001). Such mutations also indicate a poor prognosis for the patient.

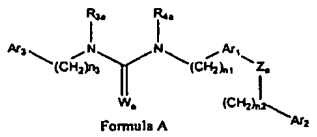
The compounds provided by the present invention are urea derivatives of substituted aryls and hetroaryls, e.g., isoxazoles, pyrazoles and isothiazoles. Urea derivatives of pyrazoles have been reported to be selective p38 kinase inhibitors by Dumas, J., et al., *Bioorg. Medic. Chem. Lett.* 10:2051-2054 (2000). Oxazoles and isopyrazoles are suggested as blockers of cytokine production in WO 00/43384 published 27 July 2000. Urea derivatives of isoxazole and pyrazoles are described as inhibitors of RAF kinase in WO 99/32106 published 1 July 1999. Such compounds are also described as p38 kinase inhibitors by Dumas, J., *et al., Bioorg. Medic. Chem. Lett.* 10:2047-2050 (2000). These compounds are also suggested as p38 kinase inhibitors in PCT publication WO 99/32111 published 1 July 1999.

There remains a need for additional compounds that are effective in inhibiting kinase activity. Given the complexities of signal transduction with the redundancy and crosstalk between various pathways, the identification of specific kinase inhibitors permits accurate targeting with limited inhibition of other pathways, thus reducing the toxicity of such inhibitory compounds.

SUMMARY OF THE INVENTION

The present invention provides compounds which modulate kinase activity, and in some embodiments inhibit protein tyrosine kinases or a specific kinase or kinase class. In some embodiments, the compositions and methods for treating and preventing conditions and diseases, such as cancer, hematologic malignancies, cardiovascular disease, inflammation or multiple sclerosis. The compounds of the invention can be delivered alone or in combination with additional agents, and are used for the treatment and/or prevention of conditions and diseases. As used throughout the specification, unless otherwise stated, each of the substituents is as previously defined.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the structure:



Formula A

wherein:

(a) R_{3a} and R_{4a} are each a suitable substituent independently selected from hydrogen, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of: halogens; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer, preferably from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH,-C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is a whole integer, preferably from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$,-, $C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$,$-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is indepenently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

or where R_{3a} and R_{4a} together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with one or more suitable substituents selected from

halogen, =O; =S; -CN; -NO_2, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and -NO_2; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -$(CH_2)_zCN$ where z is a whole integer, preferably from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -$C(NH)NH_2$, -$NHC(NH)NH_2$, -$C(S)NH_2$, -$NHC(S)NH_2$, -$NHC(O)NH_2$, -$S(O_2)H$, -S(O)H, -NH_2, -$C(O)NH_2$, -$OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -$OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -$SO_2C(O)OH$, -NHSH, -NHS(O)H, -$NHSO_2H$, -C(O)SH, -C(O)S(O)H, -$C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, -$C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, -$OC(SO_2)H$, -$S(O_2)NH_2$, -$S(O)NH_2$, -SNH_2, -$NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with oneor more suitable substituents independently selected from the group consisting of halogens, =O, -NO_2, -CN, -$(CH_2)_z$-CN where z is a whole integer, preferably from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -$C(O)NR_c$, -$C(O)OR_c$, -$C(O)R_c$, -$NR_cC(O)NR_cR_c$, -$NR_cC(O)R_c$, -$OC(O)OR_c$, -$OC(O)NR_cR_c$, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

(b) Ar_1, Ar_2 and Ar_3 are each independently an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and -NO_2; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -$(CH_2)_zCN$ where z is a whole integer, preferably from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, OOH, -$C(NH)NH_2$, -$NHC(NH)NH_2$, -$C(S)NH_2$, -$NHC(S)NH_2$, -$NHC(O)NH_2$, -$S(O_2)H$,

-S(O)H, -NH_2, -$C(O)NH_2$, -$OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -$OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -$SO_2C(O)OH$, -NHSH, -NHS(O)H, -$NHSO_2H$, -C(O)SH, -C(O)S(O)H, -$C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, -$C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, -$OC(SO_2)H$, -$S(O_2)NH_2$, -$S(O)NH_2$, -SNH_2, -$NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of halogens, =O, -NO_2, -CN, -$(CH_2)_z$-CN where z is a whole integer, preferably from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -$C(O)NR_c$, -$C(O)OR_c$, -$C(O)R_c$, -$NR_cC(O)NR_cR_c$, -$NR_cC(O)R_c$, -$OC(O)OR_c$, -$OC(O)NR_cR_c$, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

(c) n_1 is 0, 1, 2, 3 or 4;

(d) n_2 is 0, 1, 2, 3 or 4;

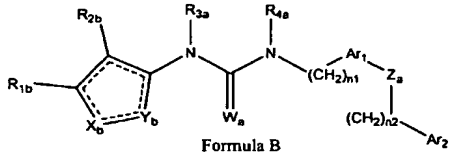
(e) n_3 is 0, 1, 2, 3 or 4;

(f) Z_a is a bond or is selected from S, O, N, NR_c, $C(O)NR_c$, $NR_cC(O)$, and CR_c, wherein R_c is a suitable substituent selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl group; and

(g) W_a is S or O;

or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, isomer derivative, or pharmaceutically acceptable solvate thereof.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the structure:



Formula B

wherein:

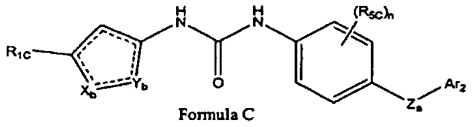
(a) X_b and Y_b are independently selected from O, N, NR_{c1}, and CR_c, wherein R_{c1} is a suitable substituent selected from hydrogen; alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl unsubstituted or substituted with one, two, or three suitable substituents, wherein X_b and Y_b are not both oxygen;

(b) R_{1b} and R_{2b} are each a suitable substitutent independently selected fromhydrogen, halogen, =O; =S; -CN; $-NO_2$, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is a whole integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is indepenently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted

cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group,

or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

Provided herein are compositions and methods for treating a disease by administering an effective amount of kinase modulating compound having the structure:



Formula C

wherein:

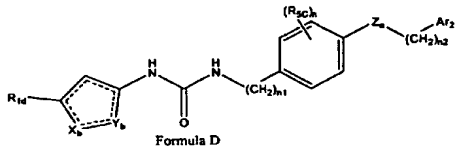
(a) R_{1C} is unsubstituted C_1-C_5 alkyl or unsubstituted C_3-C_6 cycloalkyl;

(b) n is 0, 1 or 2; and

(c) Each R_{5C} is a suitable substituent independently selected from the group consisting of halogens; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H,-OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, $-C(O)NHC(O)H$, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z 0, 1, 2, 3, or 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl,

or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

Provided herein are compositions and methods for treating a disease by administering an effective amount of kinase modulating compound having the structure:



Formula D

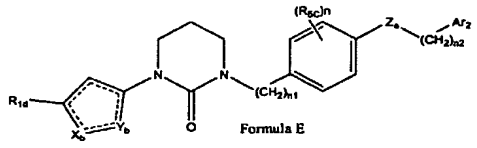
wherein:

(a) R_{1d} is unsubstituted C_1-C_5 alkyl or unsubstituted C_3-C_5 cycloalkyl;

(b) n is 0, 1 or 2;

(c) n_1 is 0, 1 or 2; and wherein n_2 is 0, 1 or 2; wherein n_1 and n_2 are not both 0.

Provided herein are compositions and methods for treating a disease by administering an effective amount of a kinase modulating compound having the structure:

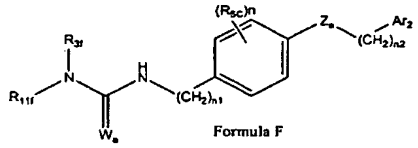


Formula E

wherein:

(a) n is 0, 1 or 2;

Provided herein are compositions and methods for treating a disease by administering an effective amount of a kinase modulating compound having the structure:



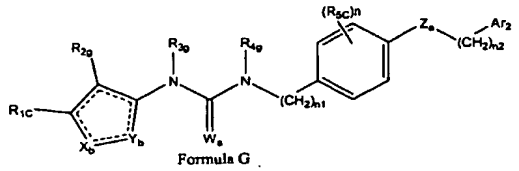
Formula F

wherein:

(a) R_{3f} and R_{11f} cyclize to form a heteroaryl or heterocycloalkyl group substituted or unsubstituted with one, two or three suitable substituents selected from the group

consisting of halogen, =O; =S; -CN; $-NO_2$, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is a whole integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



Formula G

wherein:

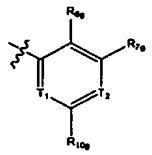
(a) R_{2g}, R_{3g} and R_{4g} are each independently selected from hydrogen, unsubstituted alkyl, unsubstituted aryl, and unsubstituted heteroaryl;

(b) n is 0, 1 or 2;

(c) n_1 is 0, 1 or 2;

(d) n_2 is 0, 1 or 2;

(e) Ar_2 is:



wherein:

(i) R_{6g} and R_{7g} cyclize to form a 5- or 6-membered aryl, heteroaryl, heterocycloalkyl or cycloakyl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of: halogens; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, $-SO_2C(O)OH$, -NHSH, NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is a whole integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$,

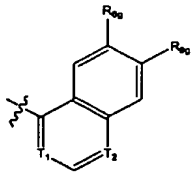
$-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

(ii) R_{10g} is a suitable substituent selected from hydrogen; halogens; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, NHS(O)H, $-NHSO_2H$, -C(O)SH, $-C(O)S(O)H$, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, =O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is a whole integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group; and

(iii) T_1 and T_2 are each independently selected from CR_w and N, where R_w is a suitable substituent selected from hydrogen; halogens; -CN; and $-NO_2$; and unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group;

or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

Compositions and methods of Formulas A-G are provided wherein X_b is O and Y_b is N and/or X_b is N and Y_b is O; and/or R_{2a}, R_{2g}, R_{3a}, R_{3g}, R_{4a} and R_{4g} are each hydrogen; and/or R_{1b}, R_{1C}, and R_{1d} are each an unsubstituted or substitued t-butyl and R_{2b} and R_{2g} are hydrogen; and/or W_a is O; and/or Z_a is C(O)NH or NHC(O); and/or n is 0. In various embodiments, T_1 is N and T_2 is N or T_1 is N and T_2 is CH. In other embodiments, Ar_2 is:



wherein:

(i) R_{8g} and R_{9g} are suitable substituents each independently selected from the group consisting of hydrogen; halogens; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, -NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, -S(O)H, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, $-OS(O_2)H$, -OS(O)H, -OSH, -SC(O)H, $-S(O)C(O)OH$, $-SO_2C(O)OH$, -NHSH, -NHS(O)H, $-NHSO_2H$, -C(O)SH, -C(O)S(O)H, $-C(O)S(O_2)H$, -C(S)H, -C(S)OH, -C(SO)OH, $-C(SO_2)OH$, -NHC(S)H, -OC(S)H, -OC(S)OH, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens,

=O, $-NO_2$, -CN, $-(CH_2)_z$-CN where z is a whole integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group; and

(ii) T_1 is N and T_2 is CH or N.

Compositions and methods of Formulas A-G are provided herein wherein R_{8g} and R_{9g} are each independently selected from the group consisting of hydrogen; halogens; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, -OH, -C(O)H, -OC(O)H, -C(O)OH, $-NH_2$, $-C(O)NH_2$, - NHC(O), $-OC(O)NH_2$,-NHC(O)H, -NHC(O)OH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group.

Compositions and methods of Fomulas A-G are provided herein wherein each R_{5C} is a suitable substituent independently selected from the group consisting of halogens; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, -OH, -C(O)H, -OC(O)H, -C(O)OH, $-NH_2$, $-C(O)NH_2$, - NHC(O), $-OC(O)NH_2$, -NHC(O)H, -NHC(O)OH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted

cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group.

Compositions and methods of Formula A are provided herein wherein Ar_3 is a 5-membered aryl, heteroaryl, heterocylcoalkyl or cycloalkyl group unsubstituted or substituted with one, two or three suitable substituents. In some embodiments, Ar_3 is a 5- or 6-membered aryl or heteroaryl group unsubstituted or substituted with one, two or three suitable substituents.

Compositions and methods of Formula A-G are provided herein wherein n_3 is 0 or 1, and/or wherein n_1 is 0, 1 or 2, and/or n_2 is 0, 1 or 2. In some embodiments, R_{3a}/R_{3g} and R_{4a}/R_{4g} are each hydrogen. In other embodiments, R_{3a}/R_{3g} and R_{4a}/R_{4g} are not both substituted.

Compositions and methods of Formula A are provided herein wherein Ar_3 a substituted or unsubstituted 5-membered heteroaryl group and R_2 is hydrogen. In some embodiments, Ar_1 is an unsubstituted or substituted 6-membered aryl group or an unsubstituted or substituted 6-membered heteroaryl group. In other embodiments, W_a is O.

Compositions and methods of Formulas A-G wherein Z_a is not carbon are described herein. In some embodiments, Z_a is selected from S, O, N, NR_{c2}, $C(O)NR_{c2}$, and $NR_{c2}C(O)$, wherein R_{c2} is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl group. In other embodiments, Z_a is C(O)NH, NHC(O), or NH.

Compositions and methods of Formulas A-G wherein W_a is S, O, or NH are described herein.

Compositions and methods of Formulas A-G are described herein wherein Ar_1 is an aryl or heteroaryl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, -OH, -C(O)H, -OC(O)H, -C(O)OH, $-NH_2$, $-C(O)NH_2$, -NHC(O), $-OC(O)NH_2$,-NHC(O)H, -NHC(O)OH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, unsubstituted alkyl, unsubstituted alkenyl,

unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl.

Compositions and methods of Formulas A-G are described herein wherein Ar_2 is an aryl, heteroaryl, heterocylcoalkyl or cycloalkyl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens; -CN; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, -OH, -C(O)H, -OC(O)H, -C(O)OH, $-NH_2$, $-C(O)NH_2$, -NHC(O), $-OC(O)NH_2$,-NHC(O)H, -NHC(O)OH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl. In some embodiments, Ar_2 is an unsubstituted or substituted pyridinyl. In other embodiments, Ar_2 is an unsubstituted or substituted quinazolinyl.

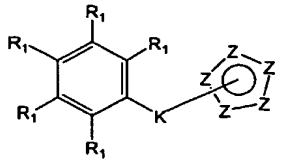
Compositions and methods of Formulas A-G are provided herein wherein X_b and Y_b are each independently selected from O, N, and NR_{c1} wherein R_{c1} is unsubstituted alkyl or unsubstituted aryl. In some emobiments, X_b is N and Y_b is NR_{c1}. In other embodiments, X_b is O and Y_b is N. In other embodiments, X_b is O and Y_b is N, or X_b is N and Y_b is O.

Compositions and methods of Formulas A-G are provided herein wherein R_1 is unsubstituted t-butyl or unsubstituted cyclopropyl.

Compositions and methods are provided herein wherein R_{5c} is independently selected from the group consisting of halogens, -CN, $-NO_2$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted heteroalkyl, unsubstituted haloalkyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl group.

Compositions and methods of Formulas A-G are provided herein wherein R_{10g} is hydrogen or lower alkyl.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



IA

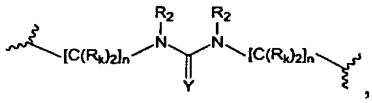
wherein:

each Z is independently C, CR_3, N, NR_3, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

where R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR_c$, $-OC(O)R_c$, $-NO_2$, $-N(R_c)_2$, $-SR_c$, $S(O)_jR_c$ where j is 1 or 2, $-NR_cC(O)R_c$, $-C(O)\ N(R_c)_2$, $-C(O)_2R_c$, or $-C(O)R_c$; or two adjacent R_1's, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

K is  , where

Y is O or S;

each R_k is independently H, halogen, substituted or unsubstituted alkyl, $-OR_2$, substituted or unsubstituted alkoxy, $-OC(O)R_2$, $-NO_2$, $-N(R_2)_2$, $-SR_2$, $-C(O)R_2$, $-C(O)_2R_2$, $-C(O)N(R_2)_2$, or $-N(R_2)C(O)R_2$;

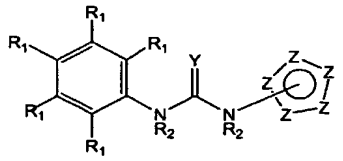
each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted

heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

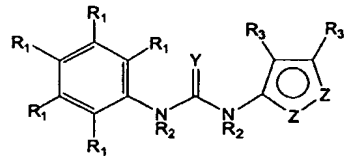
or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



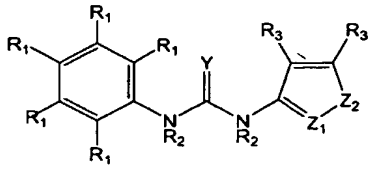
(I).

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(II).

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



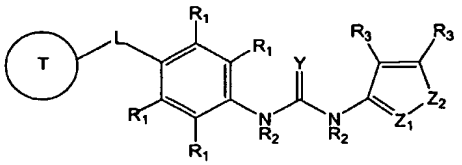
(III)

wherein:

Z_1 is CR_3 or N; and

Z_2 is O or S.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:

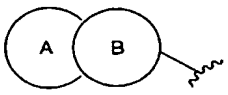


(IV)

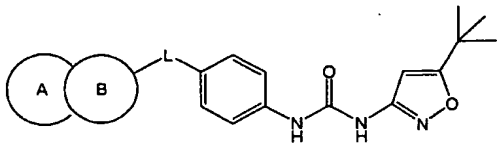
wherein:

L is a linker selected from the group consisting of a covalent bond, -(substituted or unsubstituted alkylene)-, -(substituted or unsubstituted alkenylene)-, -O-, -O(substituted or unsubstituted alkylene)-, -C(O)-, -C(O)(substituted or unsubstituted alkylene)-, -C(O)(substituted or unsubstituted alkenylene)-, -NH-, -NH(substituted or unsubstituted alkylene)-, -NH(substituted or unsubstituted alkenylene)-, –C(O)NH-, -C(O)NH(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -S-, -S(substituted or unsubstituted alkylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

T is a mono-, bi-, or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

In some embodiments, T is  wherein A is a substituted or unsubstituted five or six-membered aryl, heterocyclyl or heteroaryl; and B is a substituted or unsubstituted five or six-membered arylene, heterocyclene or heteroarylene, wherein A and B together form a fused two-ring moiety.

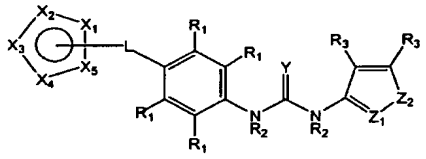
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(VI).

In some embodiments, L is –C(O)NH-. In other embodiments, B is substituted or unsubstituted phenylene, pyridinylene, pyrimidinylene, pyridazinylene, thiophenylene, imidazolylene, or pyrrolylene. In still other embodiments, L is –NH-. In yet other embodiments, B is substituted or unsubstituted phenylene, pyridinylene, pyrimidinylene, pyridazinylene, thiophenylene, or imidazolylene.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(VII)

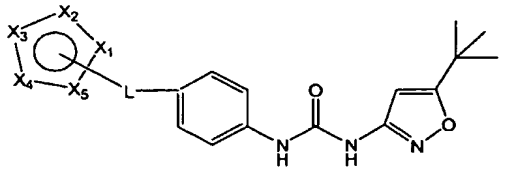
wherein:

each of X_1-X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1-X_5 is a heteroatom, and no two adjacent ring atoms are O or S; where

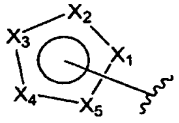
each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2, $-NR_d\,C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$, or $-C(O)R_d$, or two adjacent R_d's are taken together to form a substituted or unsubstituted aryl or hetroaryl,

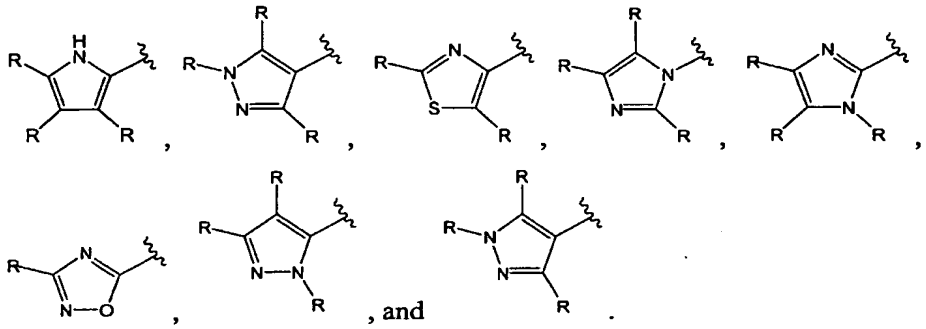
where each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:

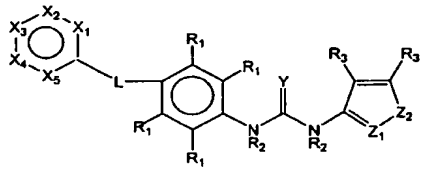


(VIII).

In some embodiemtns, L is a covalent bond, -C(O)NH-, $-OCH_2-$, or $-OCH_2CH_2-$. In other embodiments,  is selected from the group consisting of:

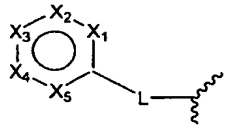


Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(IX)

wherein:

 is selected from the group consisting of:

(a) L is selected from the group consisting of -O(substituted or unsubstituted alkylene)-, and -C(O)(substituted or unsubstituted alkenylene)-; and

each of X_1-X_5 is independently CR, N-O, or N, wherein no more than two of X_1-X_5 is N, where

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-NR_dC(O)R_d$, or $-C(O)R_d$,

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(b) L is -NH-;

each of X_1, X_2, X_4, and X_5 is independently CR, N-O, or N; and

X_3 is independently CR_5 or N, wherein no more than two of X_1-X_5 is N, where

R_5 is selected from the group consisting of H, halogen, substituted or unsubstituted alkyl, substituted alkoxy, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, and $-SR_d$, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(c) L is -NH-;

each of X_1, X_3, and X_5 is independently CR, N-O, or N; and

each of X_2 and X_4 is independently CR_6 or N, wherein no more than two of X_1-X_5 is N; where

R_6 is selected from the group consisting of H, halogen, unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-C(O)R_d$, $-OC(O)R_d$,

$-NO_2$, $-N(R_d)_2$, $-SR_d$, and alkyl substituted with alkoxy, halogen, aryl, heteroaryl, amine, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, and $-SR_d$, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(d) L is –C(O)NH-;

each of X_1, X_2, X_4, and X_5 is independently CR, N-O, or N; and

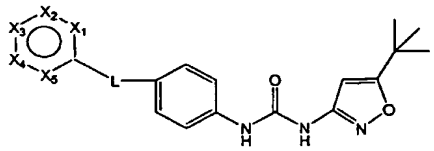
X_3 is independently CR_7 or N, wherein no more than two of X_1-X_5 is N, and

when X_3 is N, at least one of X_1, X_2, X_3, or X_5 is not CH, where

R_7 is selected from the group consisting of H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, and $-SR_d$, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

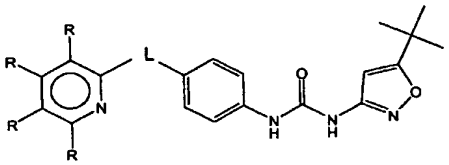
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(X).

In some embodiments, L is a linker selected from the group consisting of a covalent bond, –(substituted or unsubstituted alkylene), –NHC(O)-, -C(O)NH(substituted or unsubstituted alkylene), –NHC(O)(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene), –NHC(O)(substituted or unsubstituted alkenylene)-, and -O(substituted or unsubstituted alkylene)-.

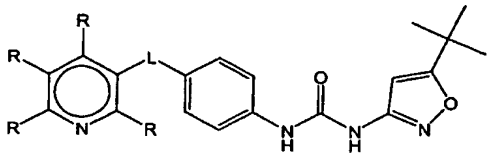
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XI).

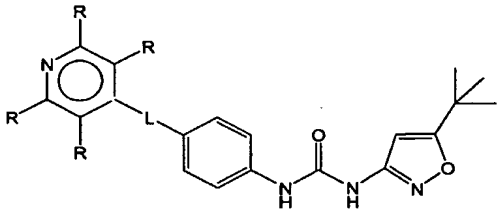
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating

compound having the following structure:



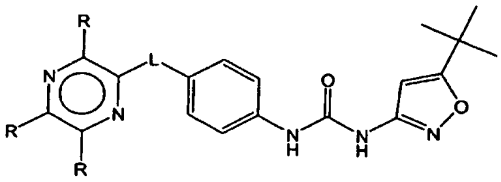
(XII).

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



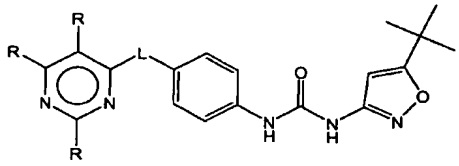
(XIII).

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XIV).

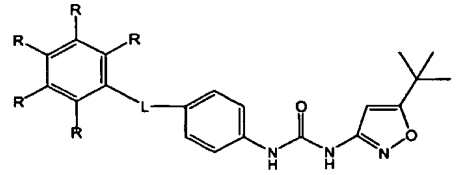
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XV).

Provided herein are compositions and methods for treating a disease comprising

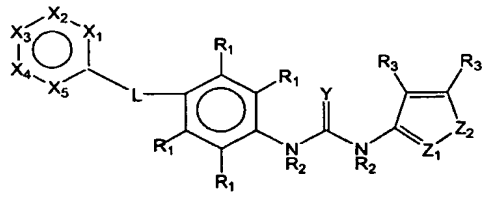
administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XVI).

In some embodiments, L is a linker selected from the group consisting of -NHC(O)-, $-OCH_2-$, $-OCH_2CH_2-$, $-NHC(O)CH_2SCH_2C(O)NH-$, -CHCHC(O)NH-, $-CHCHCH_2O-$, $-CH_2CH_2-$, and $-CH_2CH_2C(O)NH-$.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XVII)

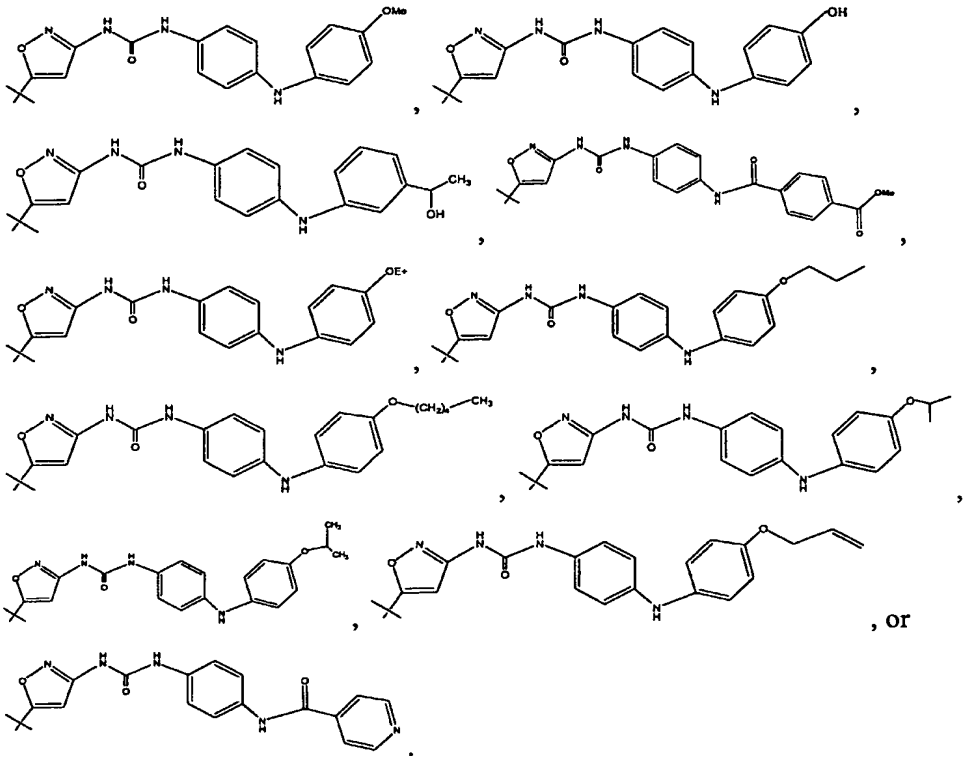
wherein:

each of X_1-X_5 is independently C, CR, N-O, or, wherein no more than two of X_1-X_5 is N; where

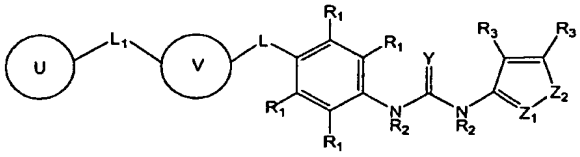
each R is independently H, halogen, substituted or unsubstituted alkyl, $-OR_d$, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2, $-NR_d\,C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$ or $-C(O)R_d$; or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl

with a proviso that said compound is not:

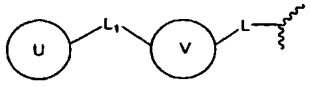


Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XVIII)

wherein:



is selected from the group consisting of:

(a) each of L and L_1 is independently a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -

(substituted or unsubstituted alkylene)-, -C(O)-, and -N(substituted or unsubstituted alkylene)-;

U is a substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene;

(b) L is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

L_1 is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, and -N(substituted or unsubstituted alkylene)-;

U is selected from the group consisting of:

(i) substituted or unsubstituted cycloalkyl;

(ii) unsubstituted aryl;

(iii) aryl substituted at any position with -Cl, -I, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -$OC(O)R_3$, $-NO_2$, $-N(R_g)_2$, $-SR_g$, $-C(O)R_h$, where R_h is H, -OH, $-N(R_g)_2$, or substituted or unsubstituted alkoxy, and where R_g is H or substituted or unsubstituted alkyl; and

(iv) substituted or unsubstituted heteroaryl, except pyridinyl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene; and

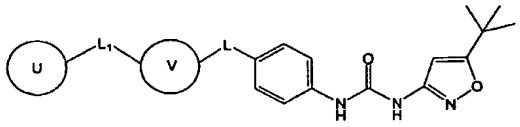
(c) L is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-,
-O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

L_1 is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted C_2-C_5 alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

U is selected from the group consisting of substituted or unsubstituted cycloalkyl; substituted aryl; and substituted or unsubstituted heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

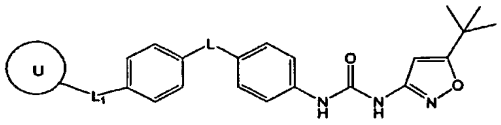
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XIX).

In some embodiments, L_1 is a bond; and L is a bond or -C(O)NH-. In other embodiments, U is substituted or unsubstituted phenyl, thiazolyl, or pyridinyl; and V is substituted or unsubstituted piperidinylene, thiazolylene, imidazolylene, or thiophenylene.

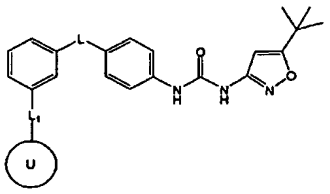
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XX).

In some embodiments, L_1 is a bond, $-CH_2O-$, $-N(CH_3)-$, or –O-; and L is $-CH_2O-$ or -NHC(O)-. In other embodiments, U is substituted or unsubstituted phenyl, C_3-C_6 cycloalkyl, pyrimidine, or pyridine.

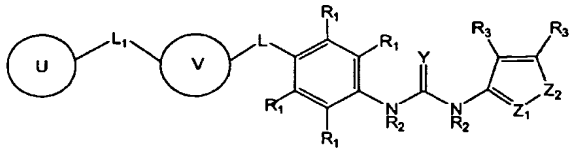
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XXI).

In some embodiments, L_1 is a -NH- or –O-; and L is -NHC(O)-. In other embodiments, U is substituted or unsubstituted pyrmidyl.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XXII)

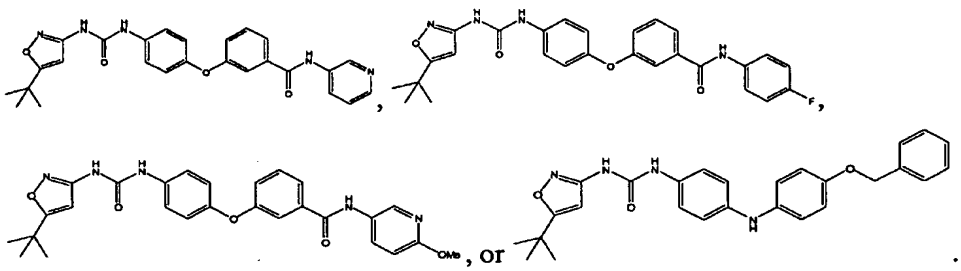
wherein:

L and L_1 is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, –C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, C(O)NH(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-;

U is a substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

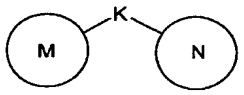
V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene;

with a proviso that said compound is not:



Exemplary FLT-3 Modulators

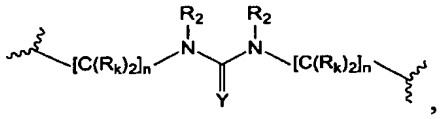
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound corresponding to the following formula are provided herein:



wherein:

M is substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

N is a substituted or unsubstituted aryl, or substituted or unsubstituted hetroaryl; and

K is 

, where

Y is O or S;

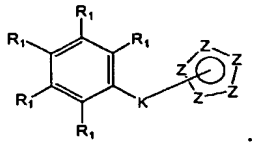
each R_k is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_2$, $-NO_2$, $-N(R_2)_2$, $-SR_2$, $-C(O)R_2$, $-C(O)_2R_2$, $-C(O)N(R_2)_2$, or $-N(R_2)C(O)R_2$,

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein:

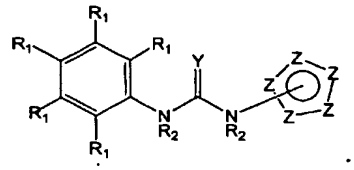
each Z is independently C, CR_3, N, NR_3, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

where R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

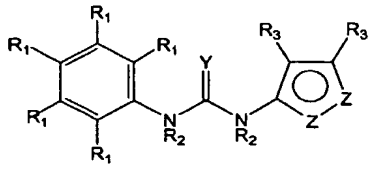
each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR_c$ -OH, $-OC(O)R_c$, $-NO_2$, $-N(R_c)_2$, $-SR_c$, $S(O)_jR_c$ where j is 1 or 2, $-NR_cC(O)R_c$, $-C(O)N(R_c)_2$, $C(O)_2R_c$, or $-C(O)R_c$; or two adjacent R_1's, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

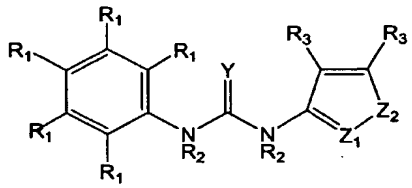
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

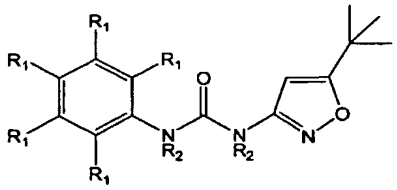


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein Z_1 is CR_3 or N; and Z_2 is O or S.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

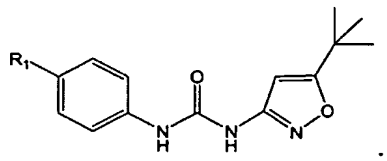


wherein:

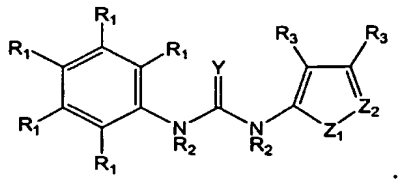
each R_1 is independently H, halogen, substituted or unsubstituted alkyl, -O(substituted or unsubstituted alkyl), -O(substituted or unsubstituted alkenyl), -$NR_cC(O)O$(substituted or unsubstituted alkyl), -$NR_cC(O)$(substituted or unsubstituted alkyl), -$NR_cC(O)$(substituted or unsubstituted alkenyl), -$C(O)NR_c$(substituted or unsubstituted alkyl), -$C(O)NR_c$(substituted or unsubstituted alkenyl), -NO_2, -$S(=O)R_c$, -SR_c, $C(O)_2R_c$, or -$C(O)R_c$; and

each R_2 is independently H or substituted or unsubstituted alkyl.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

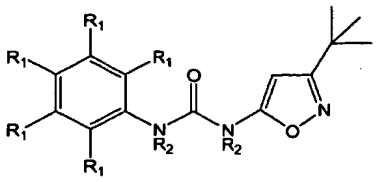


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein Z_1 is O or S; and Z_2 is CR_3 or N.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

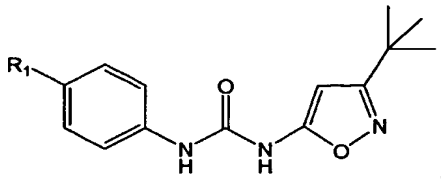


wherein:

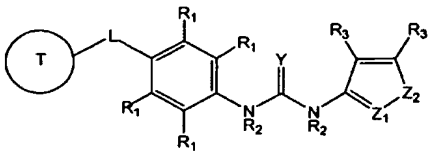
each R_1 is independently H, halogen, substituted or unsubstituted alkyl, -O(substituted or unsubstituted alkyl), -O(substituted or unsubstituted alkenyl), $-NR_cC(O)O$(substituted or unsubstituted alkyl), $-NR_cC(O)$(substituted or unsubstituted alkyl), $-NR_cC(O)$(substituted or unsubstituted alkenyl), $-C(O)NR_c$(substituted or unsubstituted alkyl), $-C(O)NR_c$(substituted or unsubstituted alkenyl), $-NO_2$, $-S(=O)R_c$, $-SR_c$, $C(O)_2R_c$, or $-C(O)R_c$; and

each R_2 is independently H or substituted or unsubstituted alkyl.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



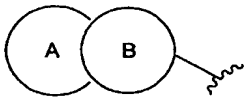
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein:

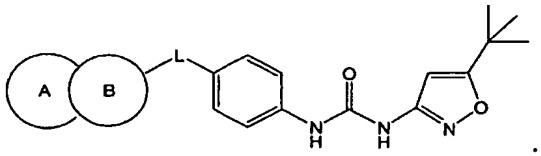
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, –C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

T is a mono-, bi, -or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

In some embodiments, T is 

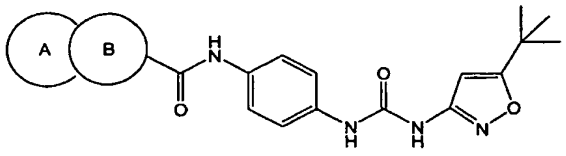
wherein A is a substituted or unsubstituted five or six-membered heterocyclyl, aryl, or heteroaryl; and B is a substituted or unsubstituted five or six-membered heterocyclene, arylene, or heteroarylene, wherein A and B together form a fused two ring moiety.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



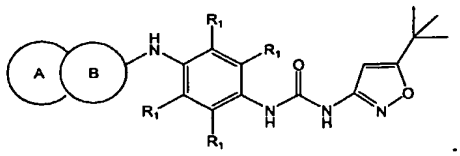
In some embodiments, L of said compound is a covalent bond, -C(O)NH(substituted or unsubstituted alkylene)-, -NHC(O)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NH-, or -O(substituted or unsubstituted alkylene)-.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



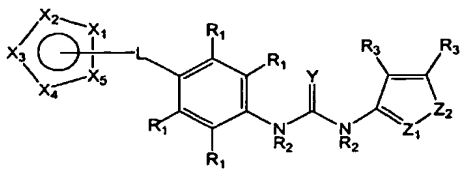
In some embodiments, B of said compound is a substituted or unsubstituted five-membered arylene or heteroarylene. In other embodiments, B is substituted or unsubstituted thiophenylene. In yet other embodiments, B is substituted or unsubstituted imidazolylene. In still other embodiments, B is substituted or unsubstituted pyrrolylene. In other embodiments, B of said compound is a substituted or unsubstituted 6-membered arylene or heteroarylene. In some embodiments, B is substituted or unsubstituted phenylene. In other embodiment, B is substituted or unsubstituted pyridinylene, pyrimidinylene, or pyridazine.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



In some embodiments, B of said compound is a substituted or unsubstituted six-membered heteroarylene. In some embodiments, said six-membered heteroarylene is substituted or unsubstituted pyrimidinylene. In other embodiments, L of said compound $-OCH_2-$. In some embodiments, L of said compound is -C(O)NH.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein:

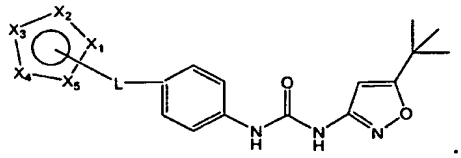
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, –C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

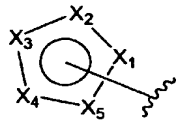
each of X_1-X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1-X_5 is a heteroatom, and no two adjacent ring atoms are O or S; where

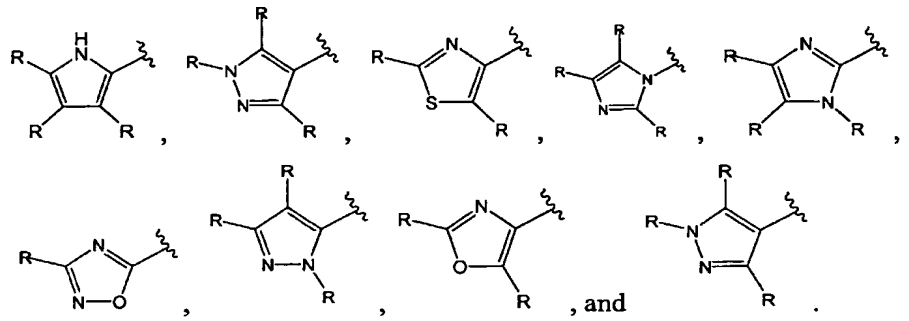
each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2, $-NR_d\,C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$ or $-C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

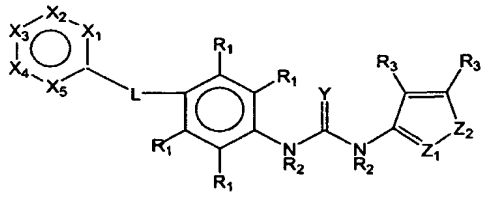
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



In some embodiments, L of said compound is a covalent bond, -C(O)NH-, or -O(substituted or unsubstituted alkylene)-. In other embodiments,  of said compound is selected from the group consisting of:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein:

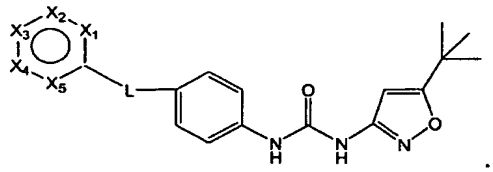
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, –C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

each of X_1-X_5 is independently C, CR,N-O, or N, wherein no more than two of X_1-X_5 is N, where

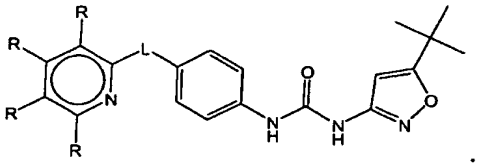
each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2, $-NR_d\,C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$ or $-C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

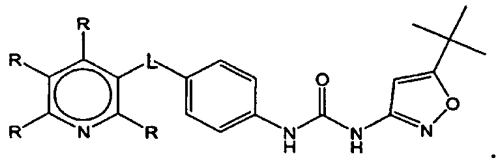
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



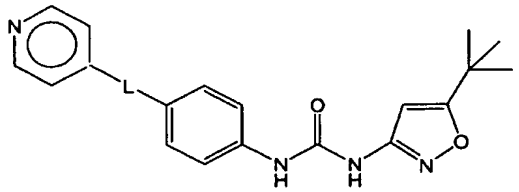
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

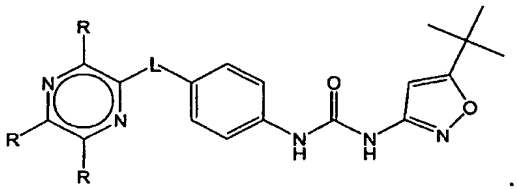


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

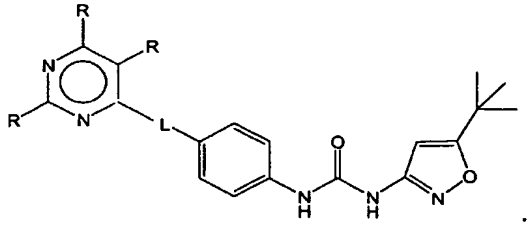


wherein L is –O(substituted or unsubstituted alkylene)- or –C(O)(substituted or unsubstituted alkenylene)-.

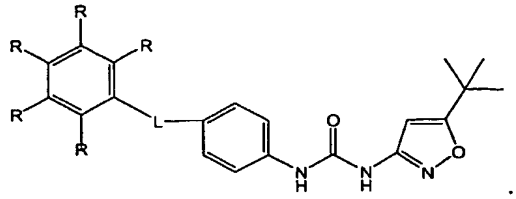
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

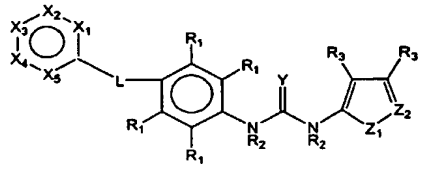


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



In some embodiments, L of said compound is -O(substituted or unsubstituted alkylene)- or -O(substituted or unsubstituted alkenylene)-. In other embodiments, L of said compound is –NHC(O)-. In yet other embodiments, L of said compound is a covalent bond, substituted or unsubstituted alkylene, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -NH(alkylene)-, -NHC(O)$CH_2SCH_2C(O)$NH-, and -NHC(O)(substituted alkylene)S-.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein:

L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, –C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-,

and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

each of X_1-X_5 is independently C, CR, or N, wherein no more than two of X_1-X_5 is N, where

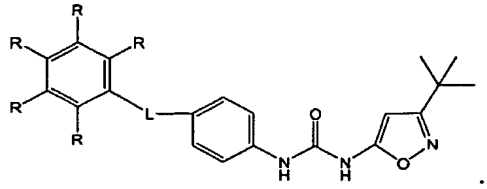
each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2, $-NR_d C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$ or $-C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

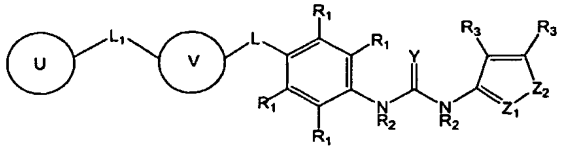
Z_1 is O or S; and

Z_2 is CR_3 or N.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



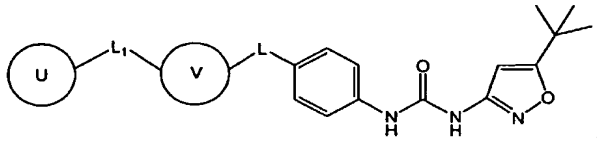
wherein:

each of L and L_1 is independently a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, –C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-;

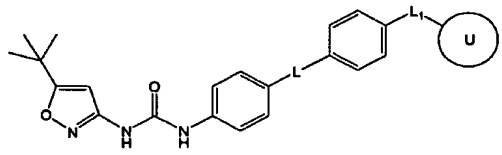
U is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

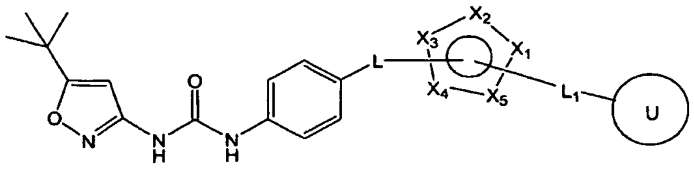


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding

to the following formula are provided herein:



wherein:

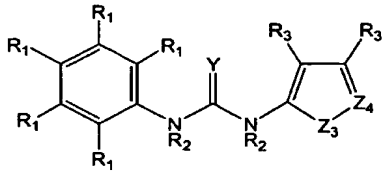
each of X_1-X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1-X_5 is a heteroatom, and no two adjacent ring atoms are O or S; and

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2, $-NR_d\,C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$ or $-C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

In some embodiments, U is a substituted or unsubstituted five-membered heteroaryl, substituted or unsubstituted phenyl, or substituted or unsubstituted six-membered heteroaryl.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



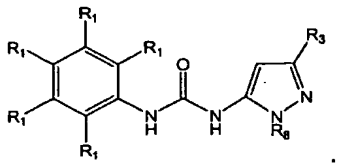
wherein:

Z_3 is NR_8, O, or S;

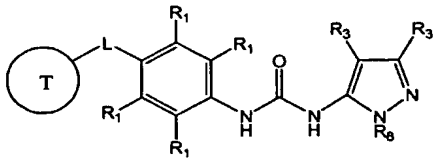
Z_4 is N or CR_8; and

R_8 is H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



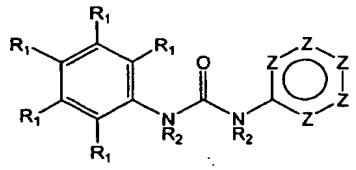
wherein:

L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, –C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

T is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

Methods for modulating FLT-3 kinase, said method comprising administering an

effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein:

each Z is independently C, CR_3, N, NR_3, O, or S, provided that no more than two Z's are heteroatoms where

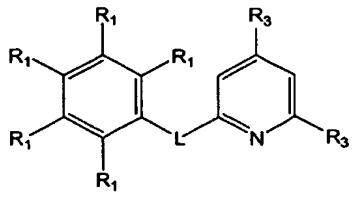
R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl.

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

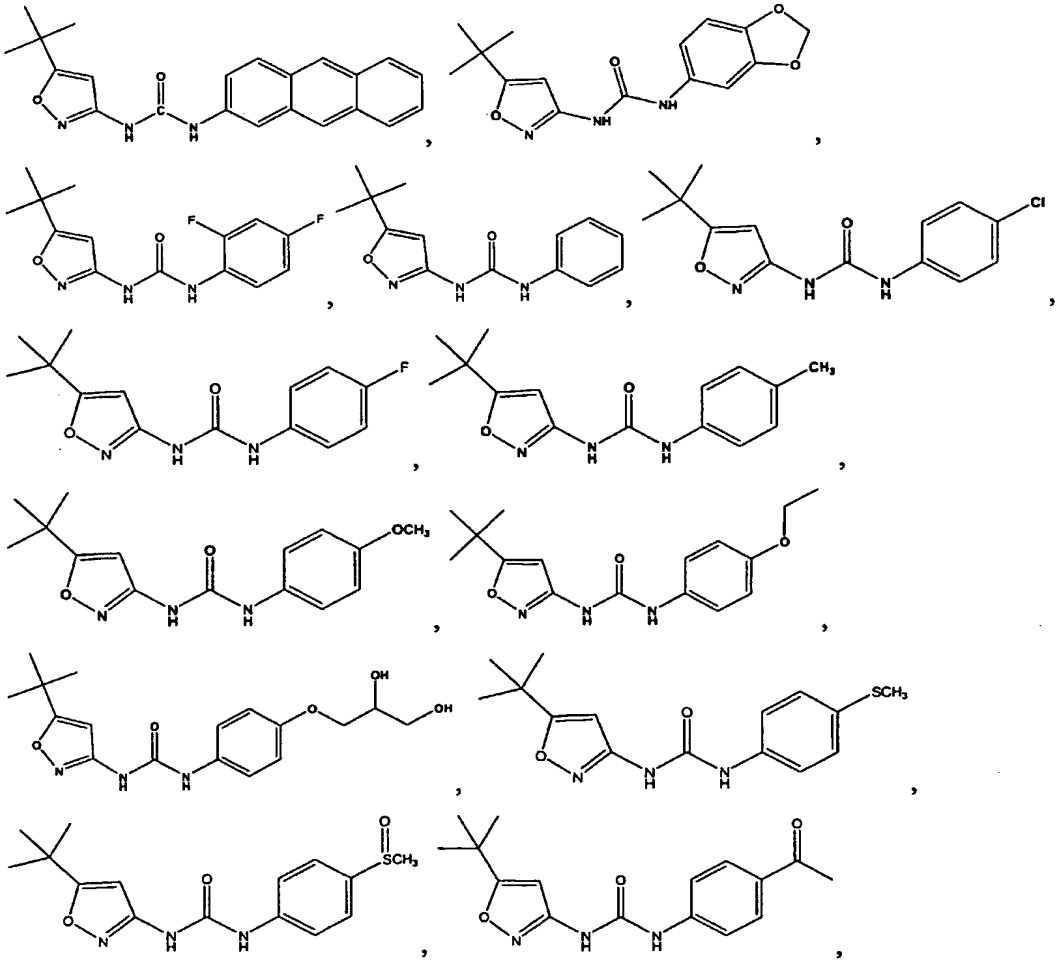
each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR_c$ -OH, $-OC(O)R_c$, $-NO_2$, $-N(R_c)_2$, $-SR_c$, $S(O)_jR_c$ where j is 1 or 2, $-NR_cC(O)R_c$, $-C(O)\ N(R_c)_2$, $C(O)_2R_c$, or $-C(O)R_c$; or two adjacent R_1's, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

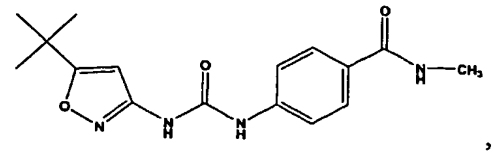
each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

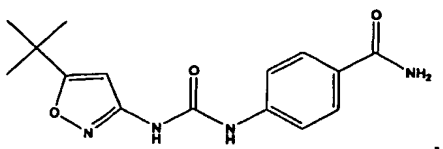
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

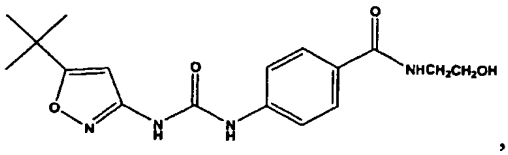


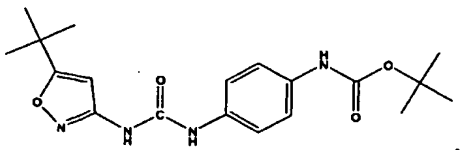
Provided herein are methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of:

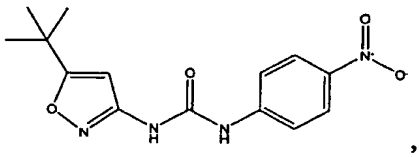


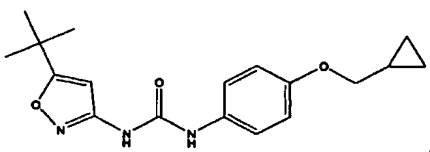


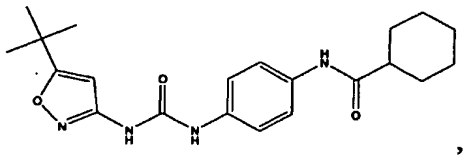


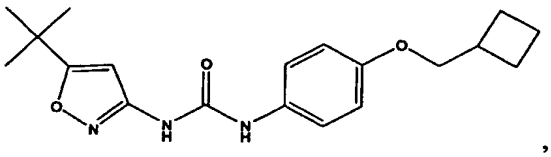


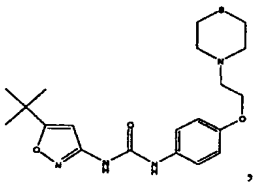


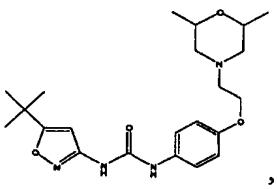


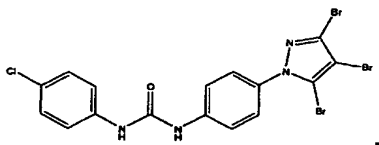


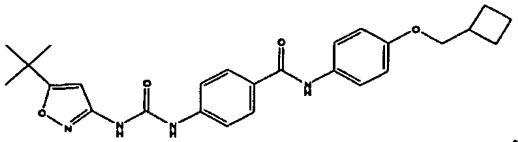


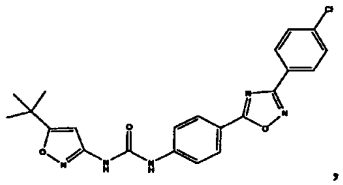


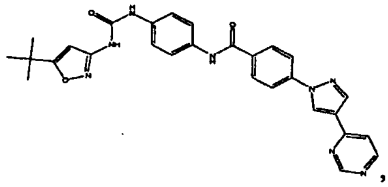


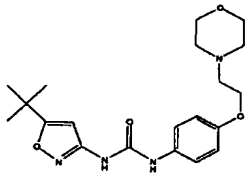


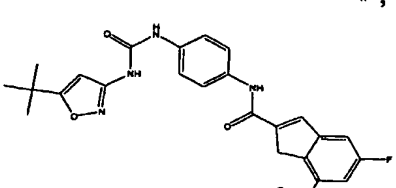


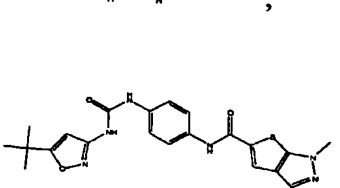


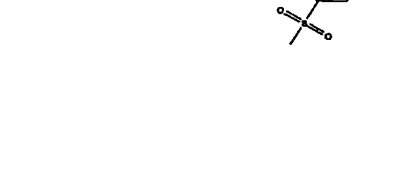












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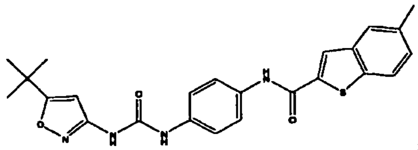
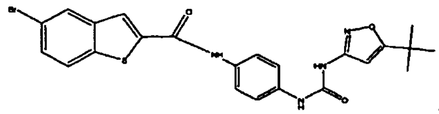
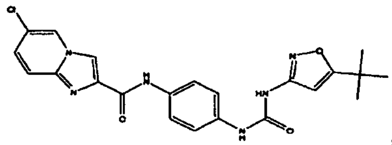
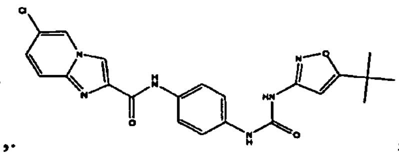
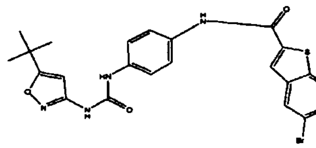
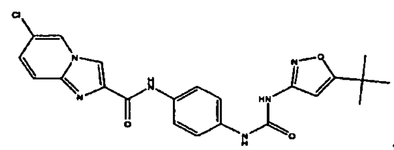
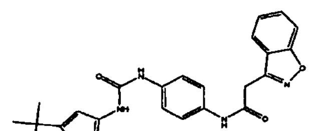
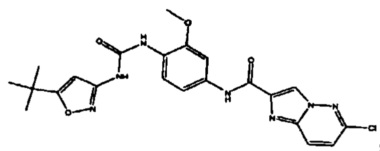
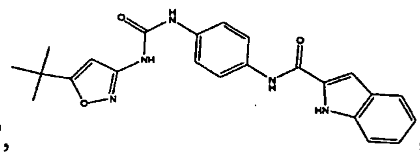
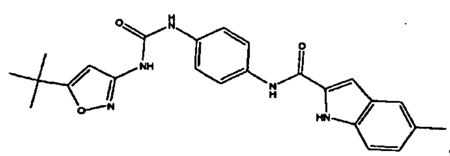
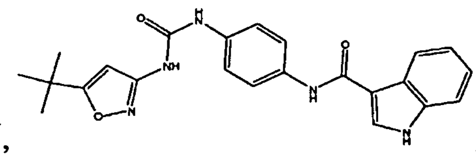
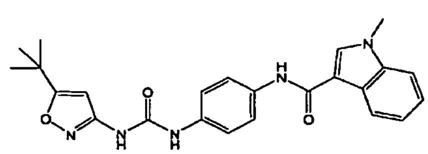
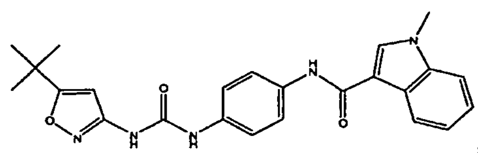
 ,  ,

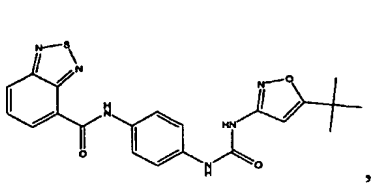
 ,.  ,

 ,  ,  ,

 ,  ,

 ,  ,

  ,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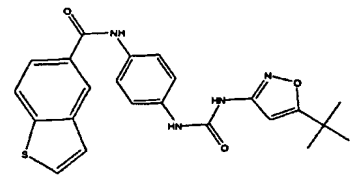
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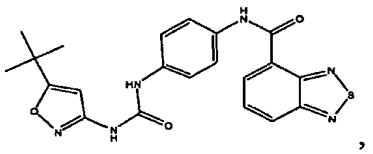
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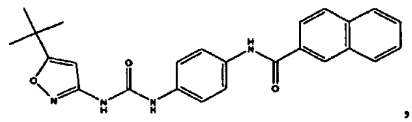
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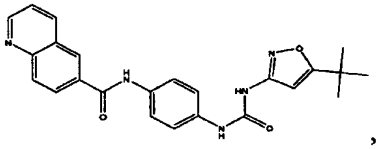
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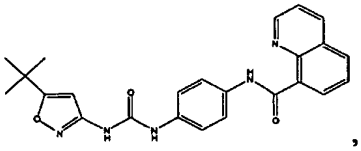
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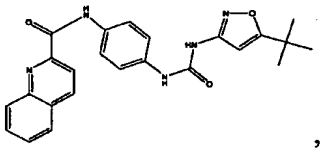
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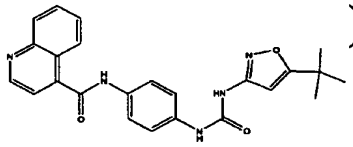
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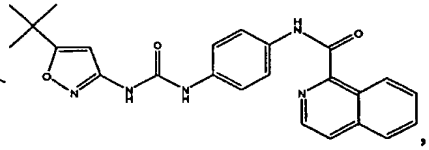
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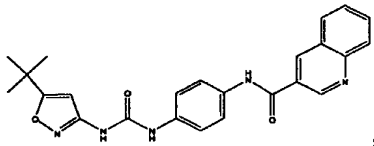
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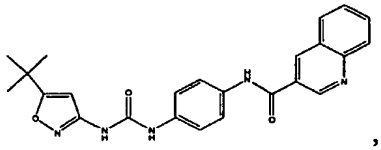
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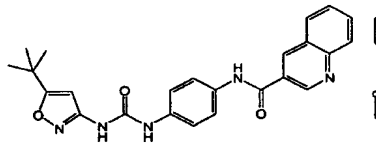
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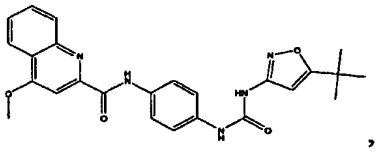
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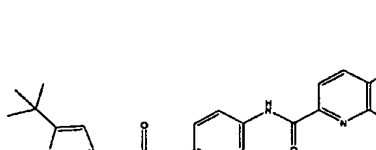
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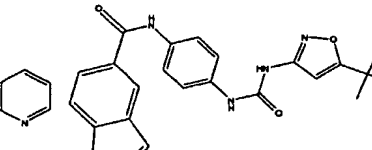
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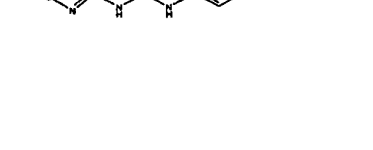
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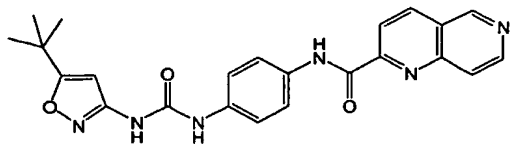
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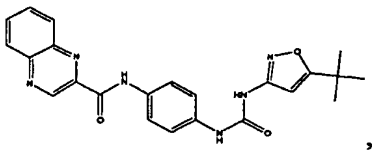
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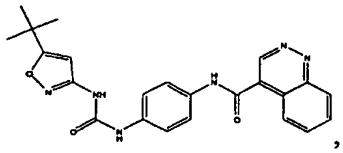
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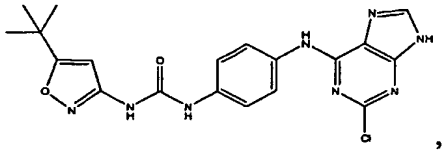
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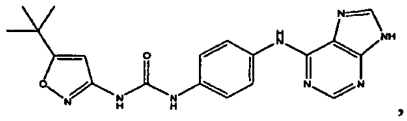
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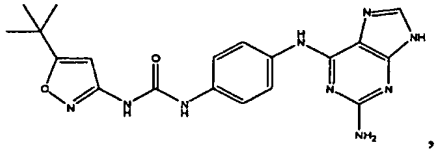
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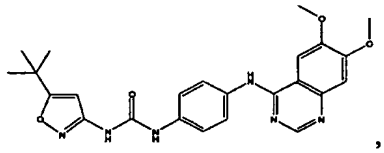
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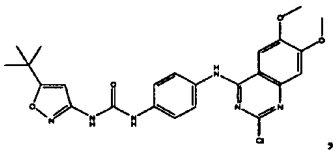
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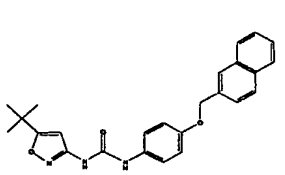
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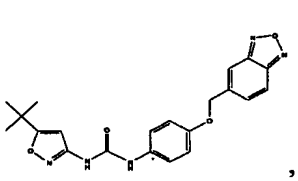
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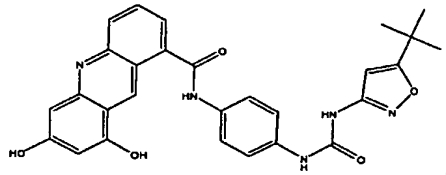
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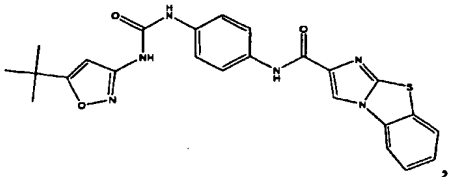
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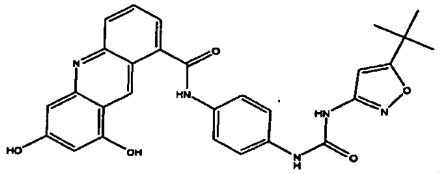
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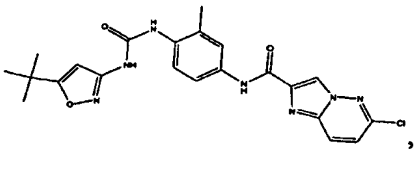
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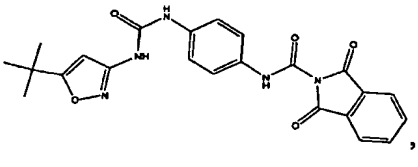
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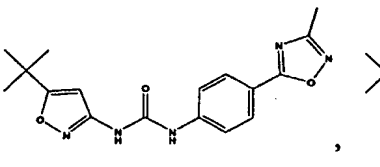
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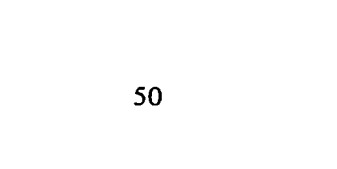
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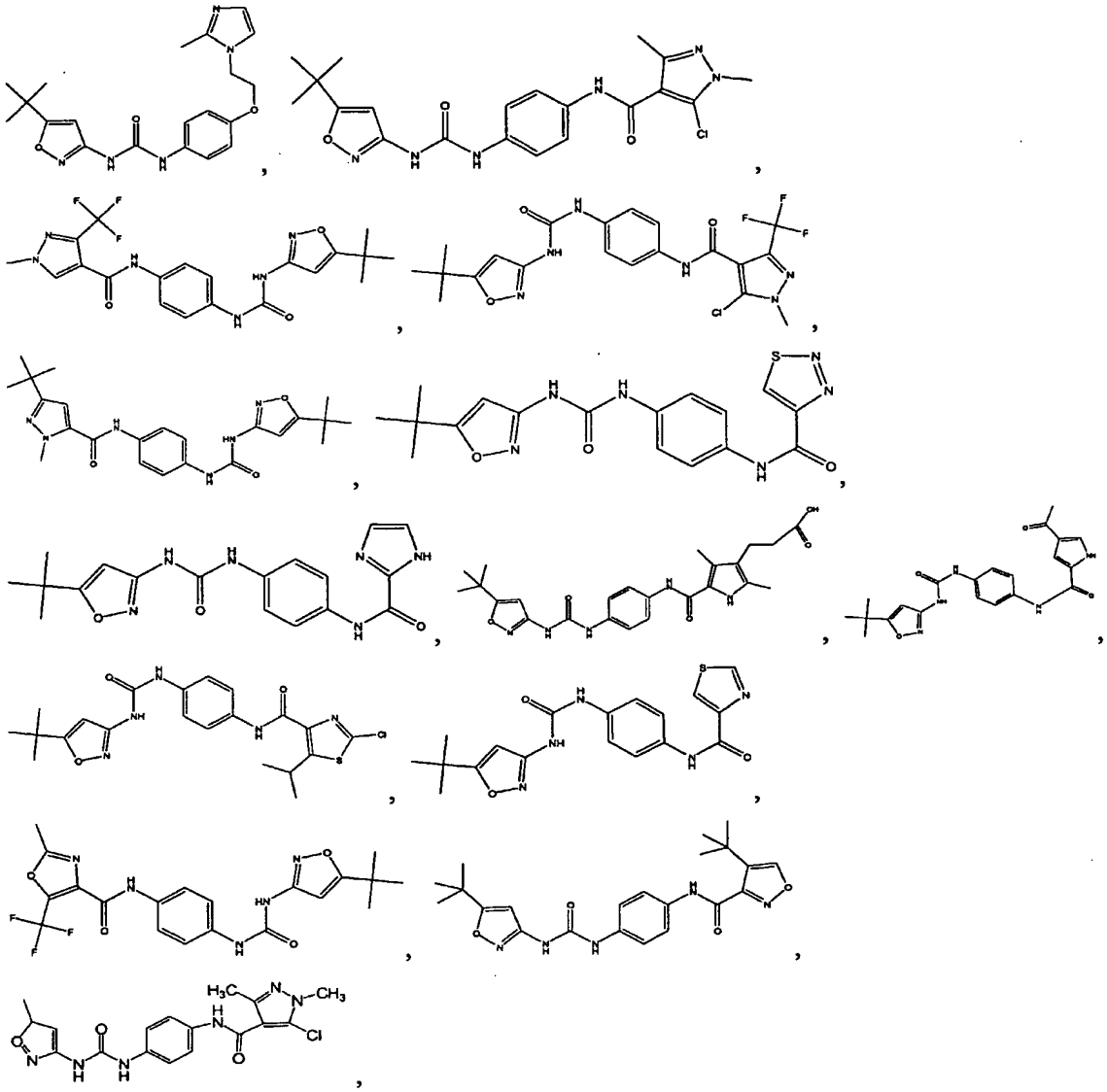

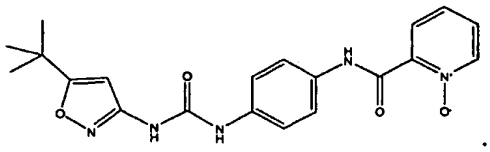

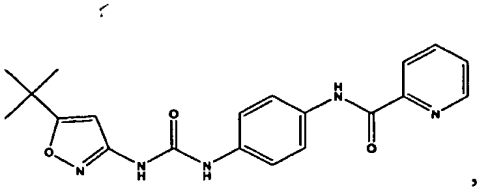

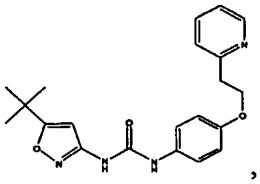

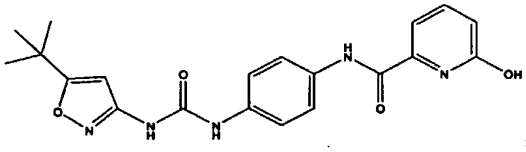

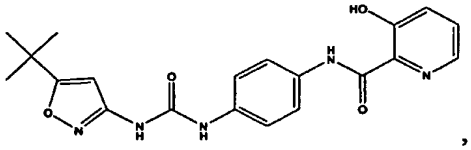

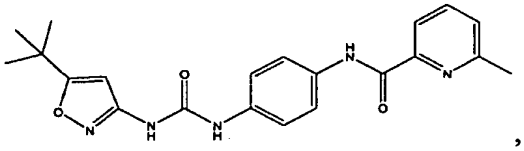

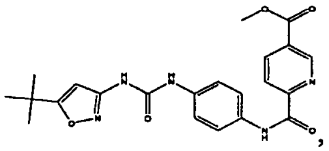

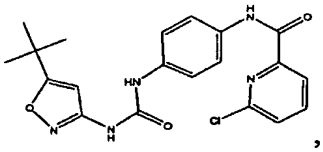

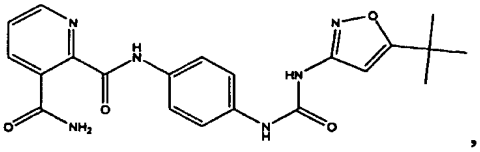

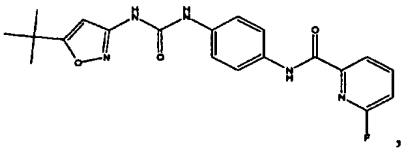

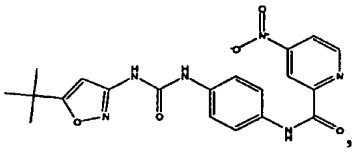

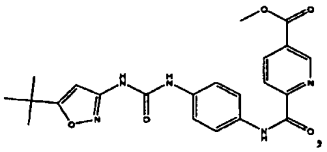

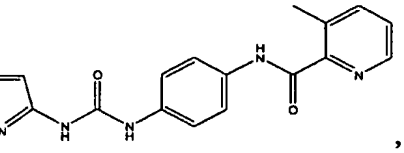

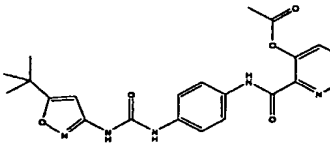

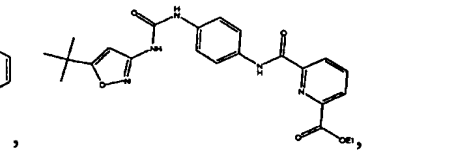

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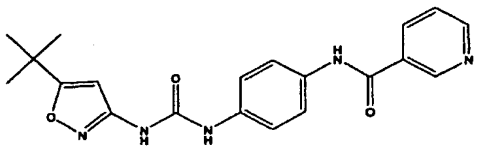
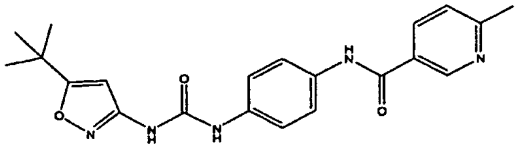
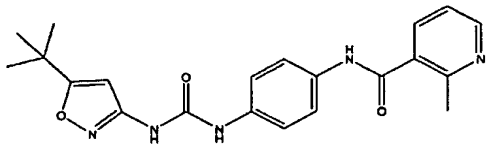
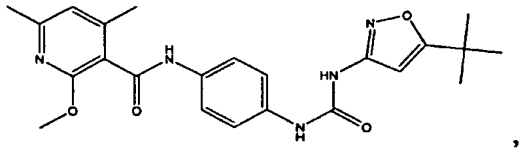
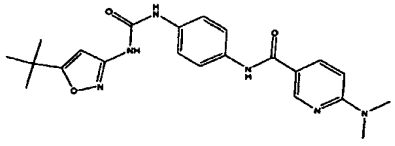
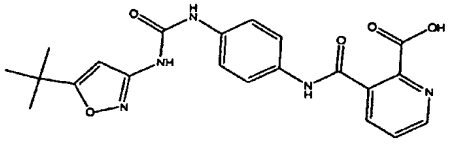
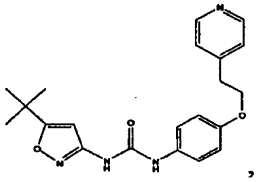
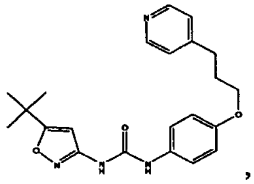
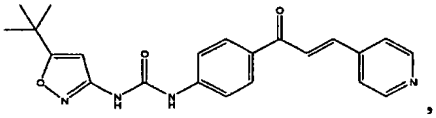
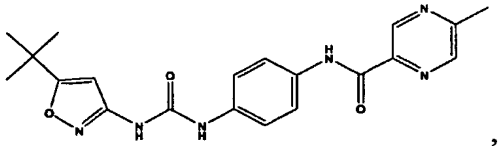
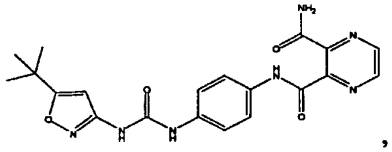
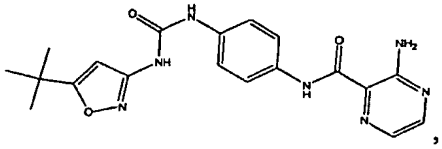
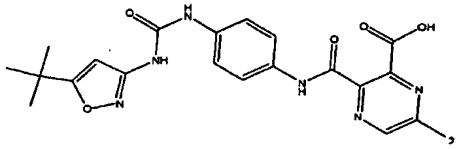
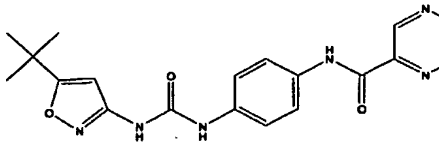
 ,
 ,
 ,
 ,
 ,
 ,,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
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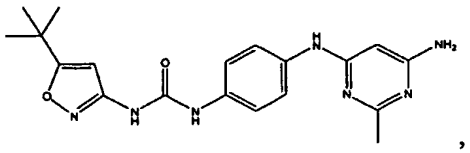
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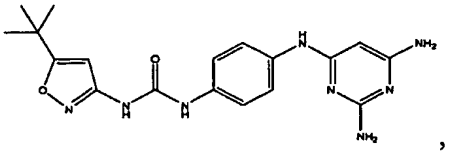
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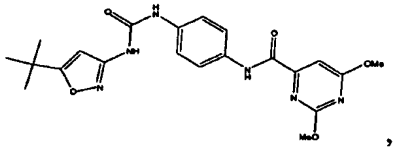
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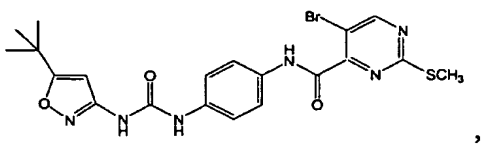
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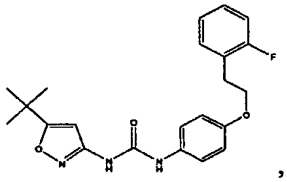
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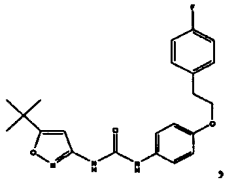
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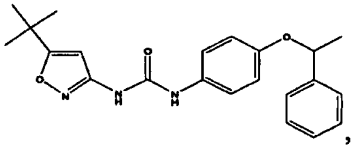
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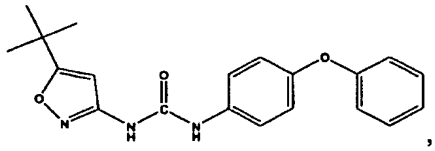
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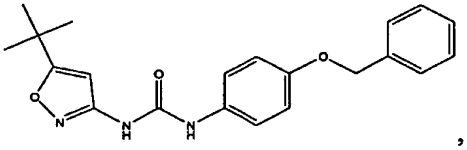
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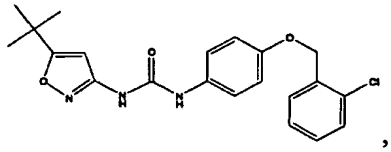
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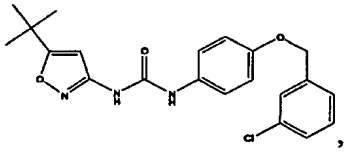
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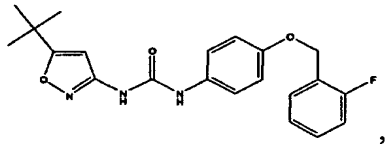
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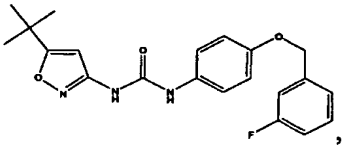
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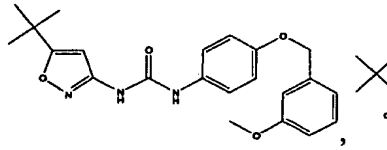
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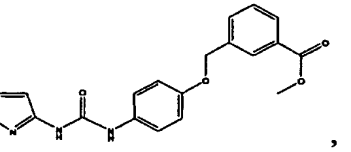
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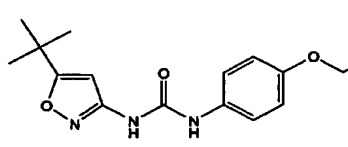
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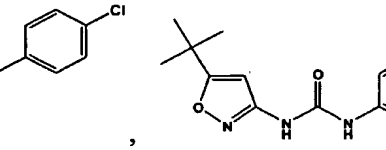
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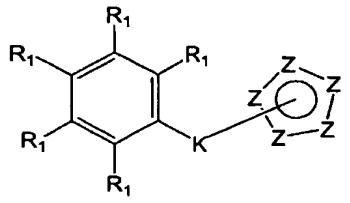
(54) Title: UREA DERIVATIVES AS KINASE MODULATORS

(57) Abstract: The invention provides methods and compositions for treating conditions mediated by various kinases wherein derivatives of urea compounds are employed. The invention also provides methods of using the compounds and/or compositions in the treatment of a variety of diseases and unwanted conditions in subjects.

WO 2005/048948 A2

WHAT IS CLAIMED IS:

1. A compound corresponding to Formula (IA):



IA

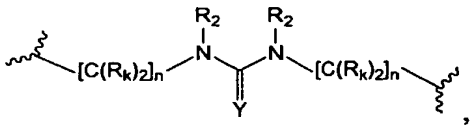
wherein:

each Z is independently C, CR_3, N, NR_3, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

where R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR_c$, $-OC(O)R_c$, $-NO_2$, $-N(R_c)_2$, $-SR_c$, $S(O)_jR_c$ where j is 1 or 2, $-NR_cC(O)R_c$, $-C(O)\ N(R_c)_2$, $-C(O)_2R_c$, or $-C(O)R_c$; or two adjacent R_1's, are taken together to form a substituted or unsubstituted aryl or heteroaryl,

each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

K is  , where

Y is O or S;

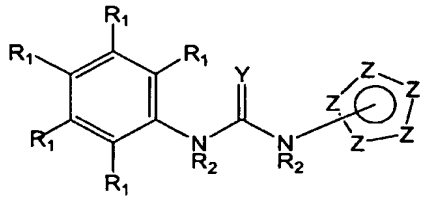
each R_k is independently H, halogen, substituted or unsubstituted alkyl, $-OR_d$, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$, or $-N(R_d)C(O)R_d$, where each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

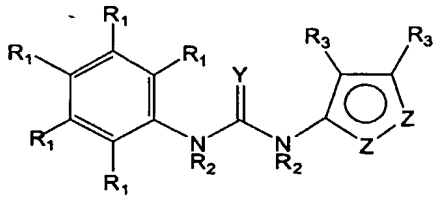
or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, corresponding to Formula (I):



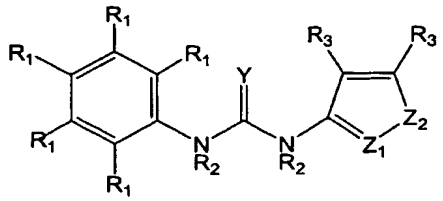
(I).

3. The compound of claim 1, corresponding to Formula (II):



(II).

4. The compound of claim 3, corresponding to Formula (III):



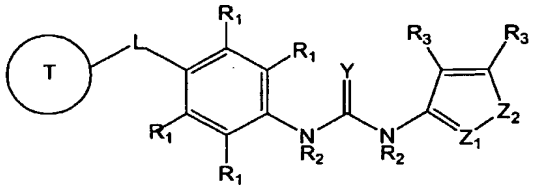
(III)

wherein:

Z_1 is CR_3 or N; and

Z_2 is O or S.

5. The compound of claim 4, corresponding to Formula (IV):



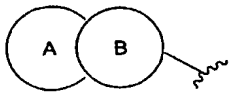
(IV)

wherein:

L is a linker selected from the group consisting of a covalent bond, -(substituted or unsubstituted alkylene)-, -(substituted or unsubstituted alkenylene)-, -O-, -O(substituted or unsubstituted alkylene)-, -C(O)-, -C(O)(substituted or unsubstituted alkylene)-, -C(O)(substituted or unsubstituted alkenylene)-, -NH-, -NH(substituted or unsubstituted alkylene)-, -NH(substituted or unsubstituted alkenylene)-, –C(O)NH-, -C(O)NH(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -S-, -S(substituted or unsubstituted alkylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

T is a mono-, bi-, or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

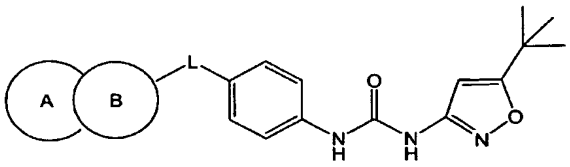
6. The compound of claim 5, wherein T corresponds to Formula (V):



(V)

wherein A is a substituted or unsubstituted five or six-membered aryl, heterocyclyl or heteroaryl; and B is a substituted or unsubstituted five or six-membered arylene, heterocyclene or heteroarylene, wherein A and B together form a fused two-ring moiety.

7. The compound of claim 6, corresponding to Formula (VI):

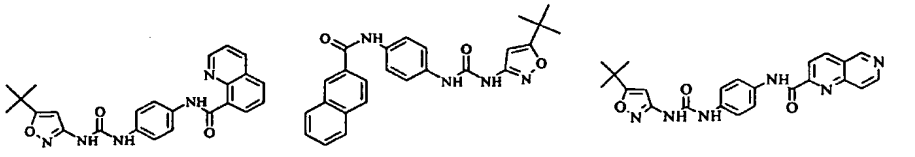


(VI).

8. The compound of claim 7, wherein L is –C(O)NH-.

9. The compound of claim 8, wherein B is substituted or unsubstituted phenylene, pyridinylene, pyrimidinylene, pyridazinylene, thiophenylene, imidazolylene, or pyrrolylene.

10. The compound of claim 9, selected from the group consisting of:



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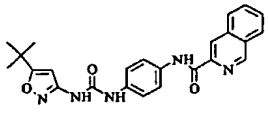
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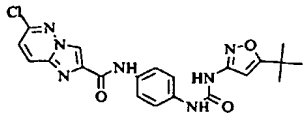
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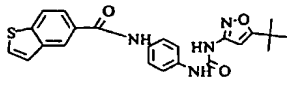
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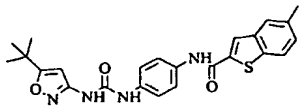
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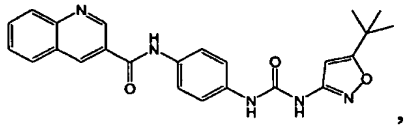
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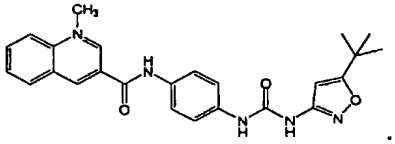
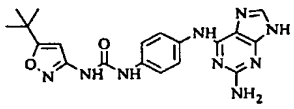

.

11. The compound of claim 7, wherein L is –NH-.

12. The compound of claim 11, wherein B is substituted or unsubstituted phenylene, pyridinylene, pyrimidinylene, pyridazinylene, thiophenylene, or imidazolylene.

13. The compound of claim 12, selected from the group consisting of: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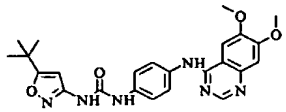
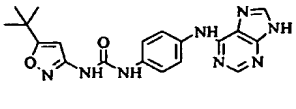

, and

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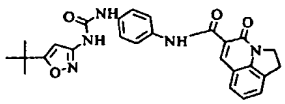
14. The compound of claim 5, corresponding to: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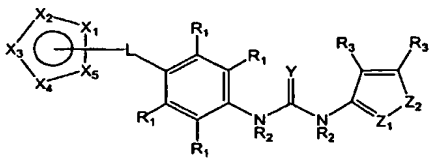
15. The compound of claim 5, corresponding to Formula (VII):



(VII)

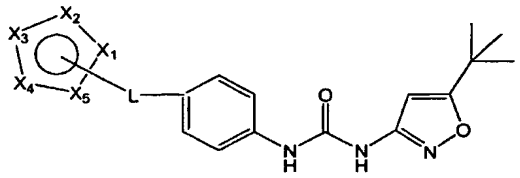
wherein:

each of X_1-X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1-X_5 is a heteroatom, and no two adjacent ring atoms are O or S; where

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2,
$-NR_d\,C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$, or $-C(O)R_d$, or two adjacent R_ds are taken together to form a substituted or unsubstituted aryl or hetroaryl,

where each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

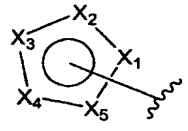
16. The compound of claim 15, corresponding to Formula (VIII):



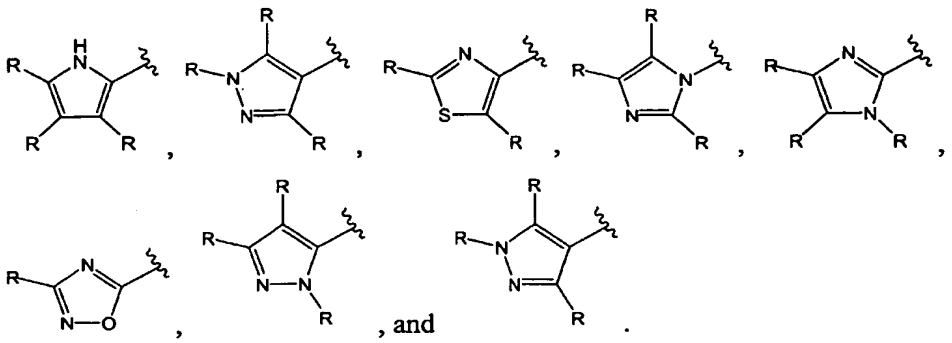
(VIII).

17. The compound of claim 16, wherein L is a covalent bond, -C(O)NH-, $-OCH_2$-, or $-OCH_2CH_2$-.

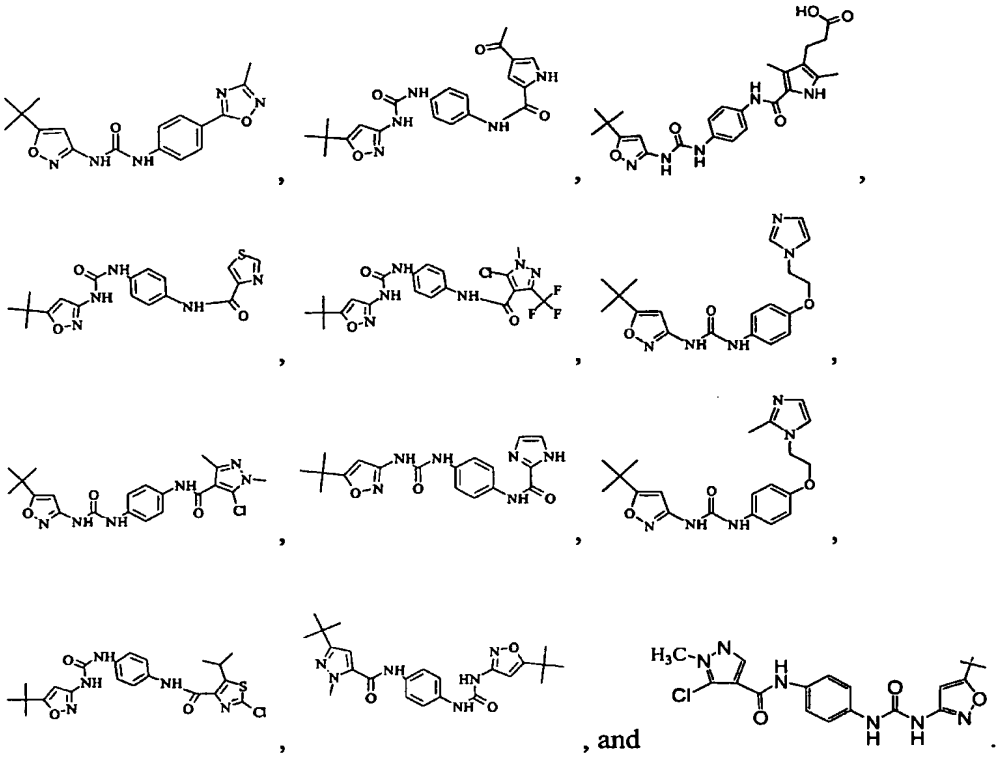
18. The compound of claim 16, wherein



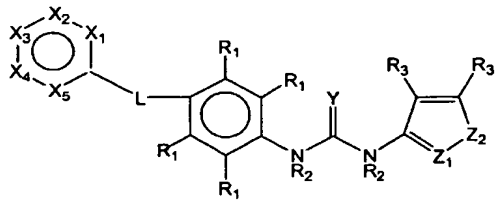
is selected from the group consisting of:



19. The compound of claim 18 selected from the group consisting of:

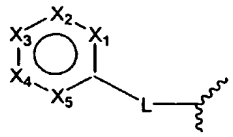


20. The compound of claim 5, corresponding to Formula (IX):



(IX)

wherein:



is selected from the group consisting of:

(a) L is selected from the group consisting of -O(substituted or unsubstituted alkylene)-, and -C(O)(substituted or unsubstituted alkenylene)-; and

each of X_1-X_5 is independently CR, N-O, or N, wherein no more than two of X_1-X_5 is N, where

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$,
$-NR_dC(O)R_d$, or $-C(O)R_d$,

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(b) L is -NH-;

each of X_1, X_2, X_4, and X_5 is independently CR, N-O, or N; and

X_3 is independently CR_5 or N, wherein no more than two of X_1-X_5 is N, where

R_5 is selected from the group consisting of H, halogen, substituted or unsubstituted alkyl, substituted alkoxy, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, and $-SR_d$, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(c) L is -NH-;

each of X_1, X_3, and X_5 is independently CR, N-O, or N; and

each of X_2 and X_4 is independently CR_6 or N, wherein no more than two of X_1-X_5 is N; where

R_6 is selected from the group consisting of H, halogen, unsubstituted alkyl,
-OH, substituted or unsubstituted alkoxy, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, and alkyl substituted with alkoxy, halogen, aryl, heteroaryl, amine, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, and $-SR_d$, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(d) L is –C(O)NH-;

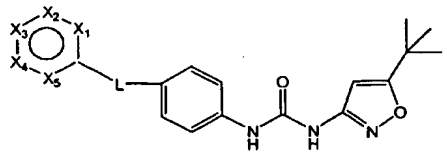
each of X_1, X_2, X_4, and X_5 is independently CR, N-O, or N; and

X_3 is independently CR_7 or N, wherein no more than two of X_1-X_5 is N, and when X_3 is N, at least one of X_1, X_2, X_3, or X_5 is not CH, where

R_7 is selected from the group consisting of H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, and $-SR_d$, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

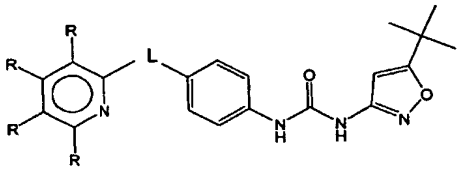
21. The compound of claim 20, corresponding to Formula (X):



(X).

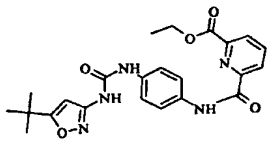
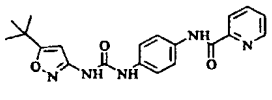
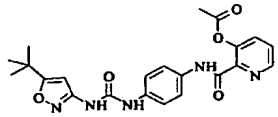
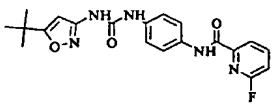
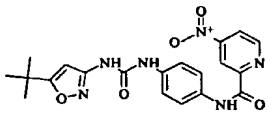
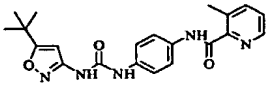
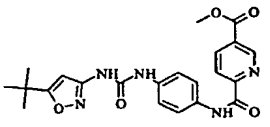
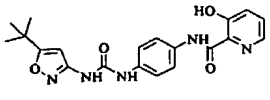
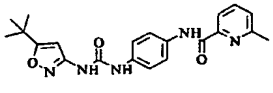
22. The compound of claim 21, wherein L is a linker selected from the group consisting of a covalent bond, –(substituted or unsubstituted alkylene), –NHC(O)-, -C(O)NH(substituted or unsubstituted alkylene), –NHC(O)(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene), –NHC(O)(substituted or unsubstituted alkenylene)-, and -O(substituted or unsubstituted alkylene)-.

23. The compound of claim 22, corresponding to Formula (XI):

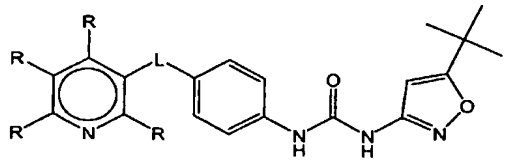


(XI).

24. The compound of claim 23, selected from the group consisting of:

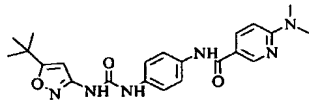

,

,

,

,

,

,

,


, and .

25. The compound of claim 21, corresponding to Formula (XII):

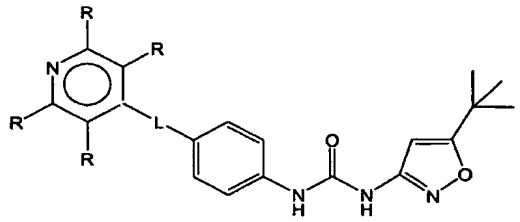


(XII).

26. The compound of claim 25, corresponding to:

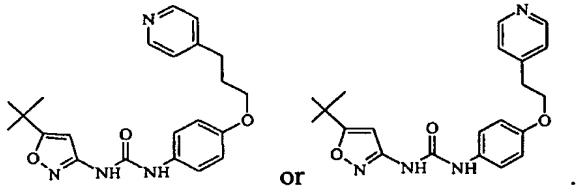


27. The compound of claim 21, corresponding to Formula (XIII):



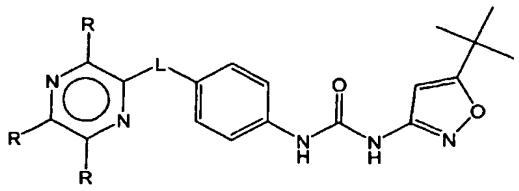
(XIII).

28. The compound of claim 27, corresponding to:



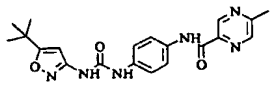
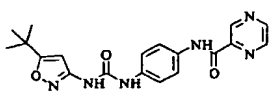
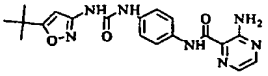
or

29. The compound of claim 21, corresponding to Formula (XIV):

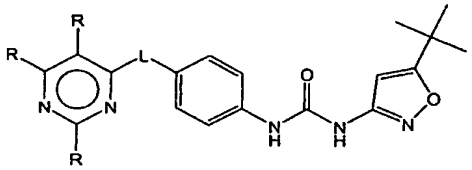


(XIV).

30. The compound of claim 29, corresponding to:

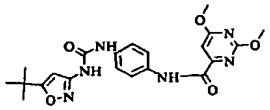

, 
, or 
.

31. The compound of claim 21, corresponding to Formula (XV):

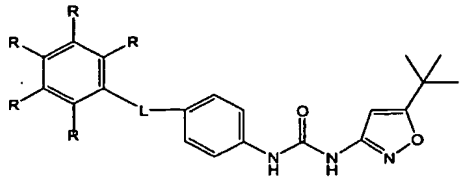


(XV).

32. The compound of claim 31, corresponding to:


.

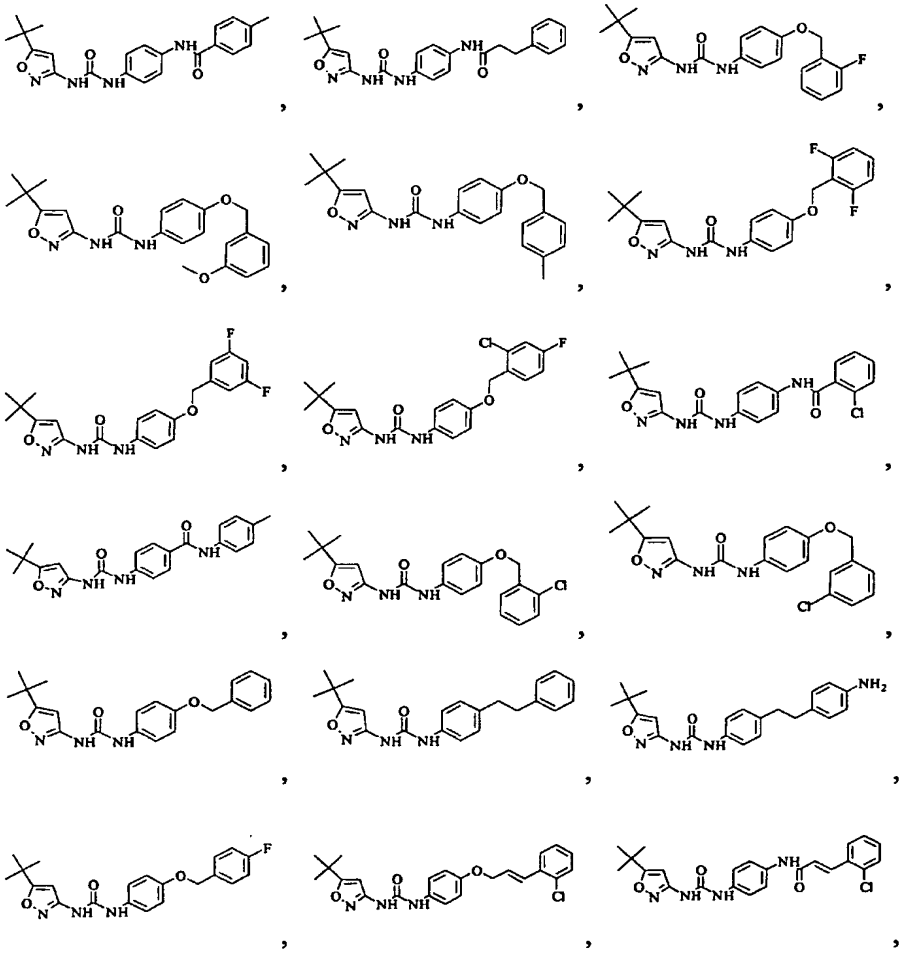
33. The compound of claim 21, corresponding to Formula (XVI):

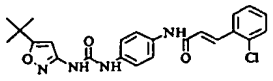
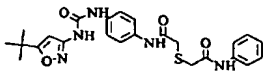
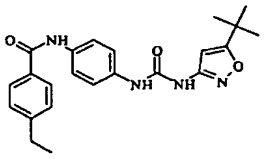


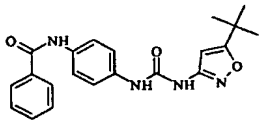
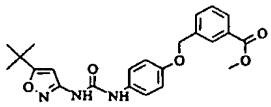
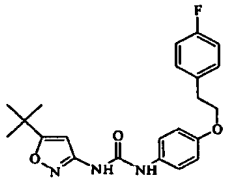
(XVI).

34. The compound of claim 33, wherein L is a linker selected from the group consisting of -NHC(O)-, -OCH_2-, -OCH_2CH_2-, -$NHC(O)CH_2SCH_2C(O)NH$-, -CHCHC(O)NH-, -$CHCHCH_2O$-, -CH_2CH_2-, and -$CH_2CH_2C(O)NH$-.

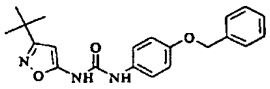
35. The compound of claim 34, selected from the group consisting of:



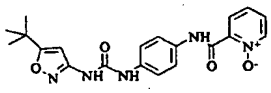

,

,

,


,

, and

.

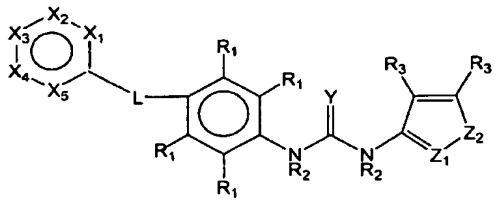
36. The compound of claim 3, corresponding to:


.

37. The compound of claim 5, corresponding to:


.

38. The compound of claim 5, corresponding to Formula (XVII):



(XVII)

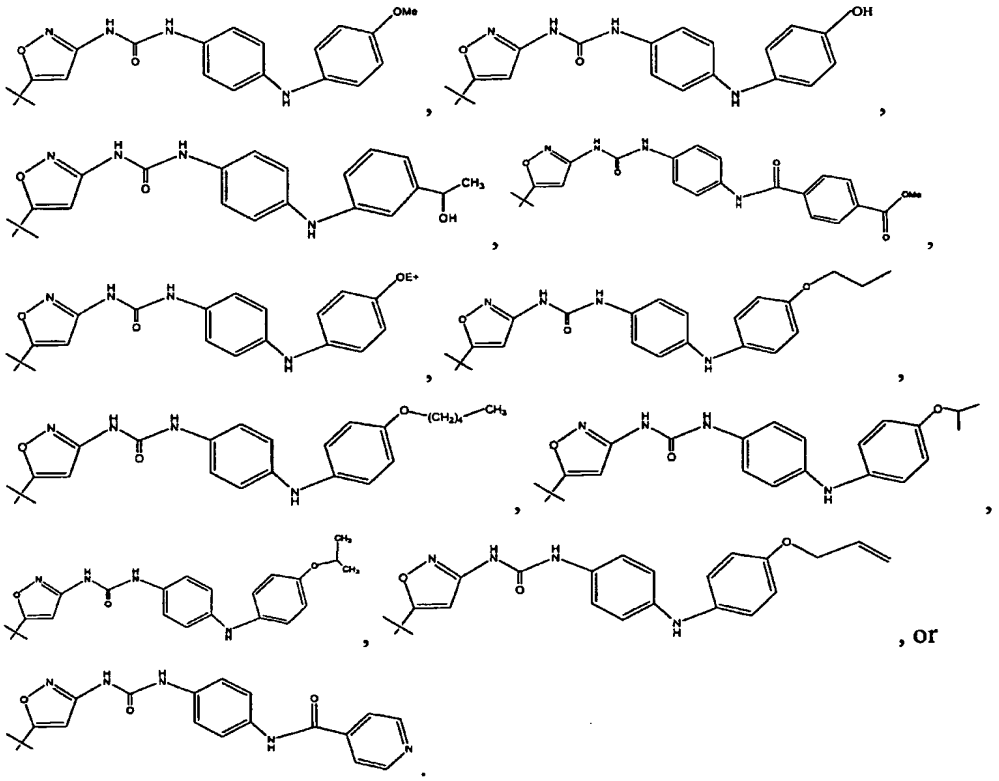
wherein:

each of X_1-X_5 is independently C, CR, N-O, or, wherein no more than two of X_1-X_5 is N; where

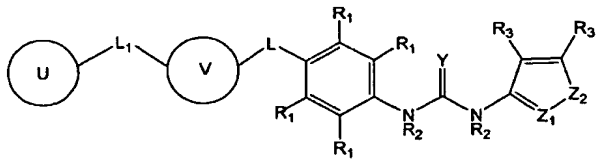
each R is independently H, halogen, substituted or unsubstituted alkyl, $-OR_d$, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2, $-NR_d\ C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$ or $-C(O)R_d$; or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl

with a proviso that said compound is not:

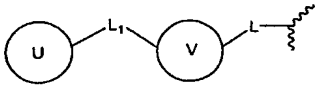


39. The compound of claim 5, corresponding to Formula (XVIII):



(XVIII)

wherein:

 is selected from the group consisting of:

(a) each of L and L_1 is independently a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -C(O)-, and -N(substituted or unsubstituted alkylene)-;

U is a substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene;

(b) L is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-,

-NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

L_1 is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-,

-NH-, -C(O)-, and -N(substituted or unsubstituted alkylene)-;

U is selected from the group consisting of:

(i) substituted or unsubstituted cycloalkyl;

(ii) unsubstituted aryl;

(iii) aryl substituted at any position with -Cl, -I, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_3$, $-NO_2$, $-N(R_g)_2$, $-SR_g$, $-C(O)R_h$, where R_h is H, -OH, $-N(R_g)_2$, or substituted or unsubstituted alkoxy, and where R_g is H or substituted or unsubstituted alkyl; and

(iv) substituted or unsubstituted heteroaryl, except pyridinyl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene; and

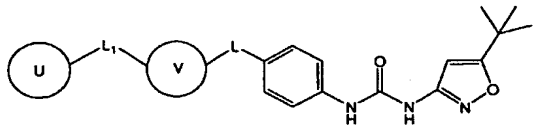
(c) L is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

L_1 is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted C_2-C_5 alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

U is selected from the group consisting of substituted or unsubstituted cycloalkyl; substituted aryl; and substituted or unsubstituted heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

40. The compound of claim 39, corresponding to Formula (XIX):

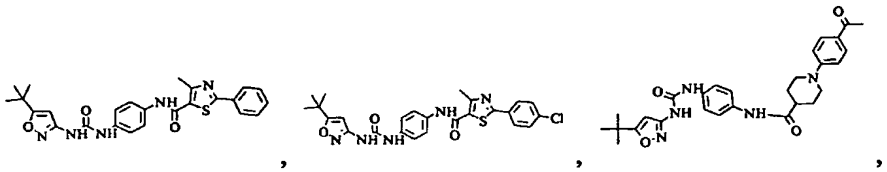


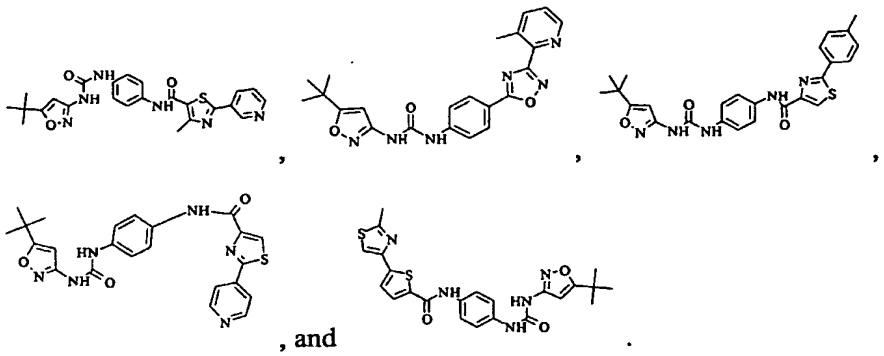
(XIX).

41. The compound of claim 40, wherein L_1 is a bond; and L is a bond or -C(O)NH-.

42. The compound of claim 41, wherein U is substituted or unsubstituted phenyl, thiazolyl, or pyridinyl; and V is substituted or unsubstituted piperidinylene, thiazolylene, imidazolylene, or thiophenylene.

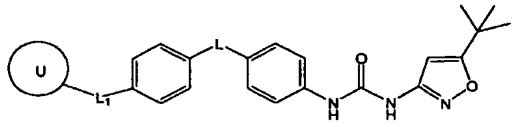
43. The compound of claim 42, selected from the group consisting of:





, and .

44. The compound of claim 40, corresponding to Formula (XX):

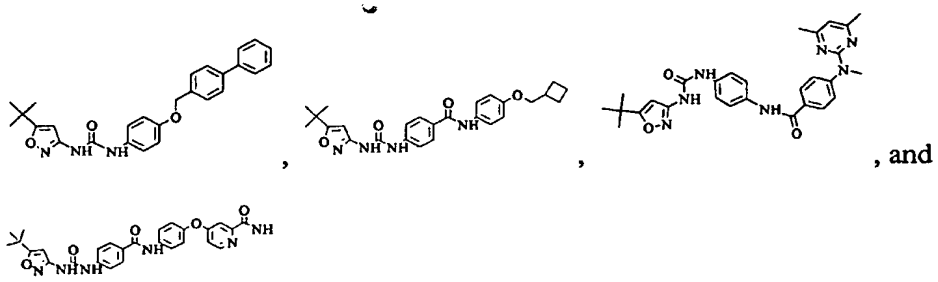


(XX).

45. The compound of claim 44, wherein L_1 is a bond, -CH_2O-, -$N(CH_3)$-, or –O-; and L is -CH_2O- or -NHC(O)-.

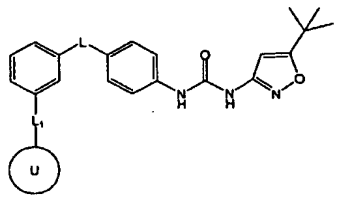
46. The compound of claim 45, wherein U is substituted or unsubstituted phenyl, C_3-C_6 cycloalkyl, pyrimidine, or pyridine.

47. The compound of claim 46, selected from the group consisting of:



, and .

48. The compound of claim 40, corresponding to Formula (XXI):

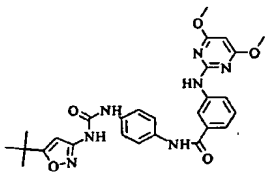
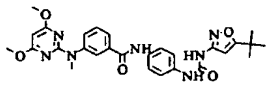
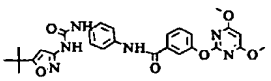


(XXI).

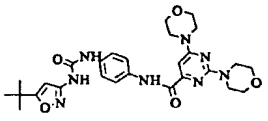
49. The compound of claim 48, wherein L_1 is a -NH- or –O-; and L is -NHC(O)-.

50. The compound of claim 49, wherein U is substituted or unsubstituted pyrmidyl.

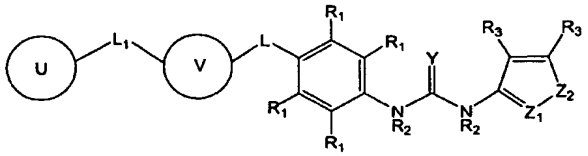
51. The compound of claim 50, selected from the group consisting of:


,

, and

.

52. The compound of claim 40, corresponding to:


.

53. The compound of claim 5, corresponding to Formula (XXII):



(XXII)

wherein:

L_1 is a linker selected from the group consisting of a covalent bond, -(substituted or unsubstituted alkylene)-, -(substituted or unsubstituted alkenylene)-, -O-,

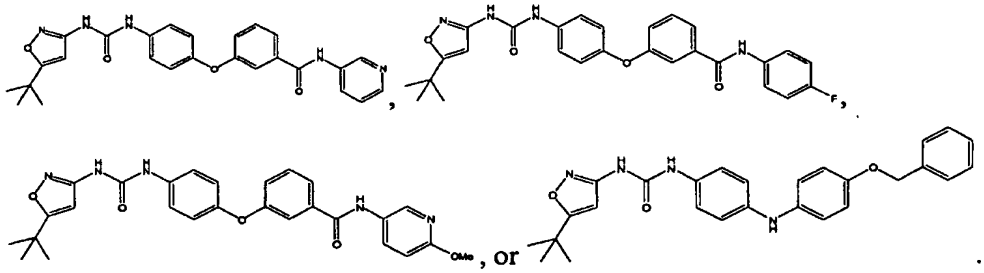
-O(substituted or unsubstituted alkylene)-, -C(O)-, -C(O)(substituted or unsubstituted alkylene)-, -C(O)(substituted or unsubstituted alkenylene)-, -NH-, -NH(substituted or unsubstituted alkylene)-, -NH(substituted or unsubstituted alkenylene)-, –C(O)NH-, -C(O)NH(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -S-, -S(substituted or unsubstituted alkylene)-, and

-NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-;

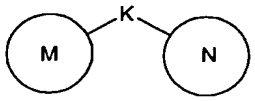
U is a substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene;

with a proviso that said compound is not:



64. A method of modulating a kinase, said method comprising administering an effective amount of a compound corresponding to Formula (IB):

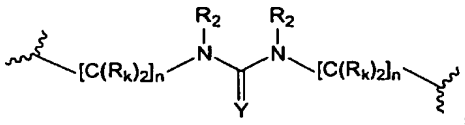


(IB)

wherein:

M is a substituted or unsubstituted heteroaryl or substituted or unsubstituted aryl;

N is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; and

K is  , where

Y is O or S;

each R_k is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_2$, $-C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$, or $-N(R_d)C(O)R_d$, where each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2's are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

65. The method of claim 64, wherein said kinase is c-kit.

66. The method of claim 64, wherein said kinase is abl.

67. The method of claim 64, wherein said kinase is p38.

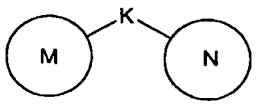
68. The method of claim 64, wherein said kinase is MKNK2.

69. The method of claim 64, wherein said kinase is flt-3.

70. The method of claim 64, wherein said kinase is PDGFR.

71. The method of claim 64, wherein said kinase is STK-10.

72. A method of treating a cellular proliferative disorder, said method comprising administering a therapeutically effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to Formula (IB):



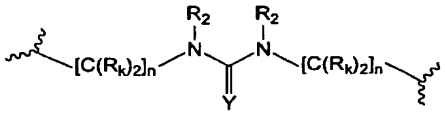
(IB)

wherein:

M is a substituted or unsubstituted heteroaryl or substituted or unsubstituted aryl;

N is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

and

K is 

, where

Y is O or S;

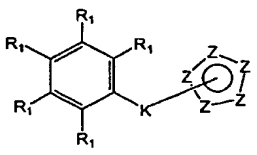
each R_k is independently H, halogen, substituted or unsubstituted alkyl, -OR_d, substituted or unsubstituted alkoxy, -$OC(O)R_d$, -NO_2, -$N(R_d)_2$, -SR_d, -$C(O)R_d$, -$C(O)_2R_d$, -$C(O)N(R_d)_2$, or -$N(R_d)C(O)R_d$, where each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3, or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer pharmaceutically acceptable salt or solvate thereof.

73. The method of claim 72, wherein said compound corresponds to Formula (IA):



(IA)

wherein:

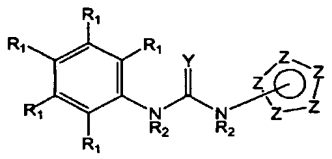
each Z is independently C, CR_3, N, NR_3, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

where R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR_c$, $-OC(O)R_c$, $-NO_2$, $-N(R_c)_2$, $-SR_c$, $-S(O)_jR_c$ where j is 1 or 2, $-NR_cC(O)R_c$, $-C(O)N(R_c)_2$, $-C(O)_2R_c$, or $-C(O)R_c$; or two adjacent R_1's, are taken together to form a substituted or unsubstituted aryl or heteroaryl,

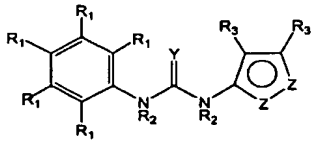
each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

74. The method of claim 73, wherein said compound corresponds to Formula (I):



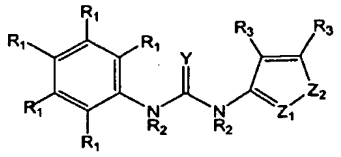
(I).

75. The method of claim 74, wherein said compound corresponds to Formula (II):



(II).

76. The method of claim 75, wherein said compound corresponds to Formula (III):



(III)

wherein Z_1 is CR_3 or N; and Z_2 is O or S.